A.M.A. Archives of OPHTHALMOLOGY

JULY 1956

VOLUME 56 NUMBER 1

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William M. Upholt, Griffith E. Quinby, Gordon S. Batchelor, and James P. Thompson

Strabismus
Marshall M. Parks

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BIFOCAL TROUBLES

How many times have the legitimate complaints of a new bifocal wearer been brushed aside by the optician—forcing the patient to take his problems to the ophthalmologist, who will, in many cases, have to find the optician's mistakes. The following is a list of the most common mechanical defects of bifocal lenses which we believe will aid the ophthalmologist in finding the source of his patient's complaints.

1. Check the DISTANCE CENTERS to be sure they coincide with the patient's distance PD horizontally and *vertically*.

2. Examine the patient's eyes for both VERTICAL and HORIZONTAL ASYMMETRY and ascertain that any difference is incorporated in the position of the bifocal.

3. Hyperopes must have ADDITIONAL DECENTRATION of the bifocal segment to compensate for the base out prism created by the distance portion of the lens.

4. Incorrect BIFOCAL HEIGHT is probably the most common problem of bifocal wearers. Segments cause trouble when fitted either too high or too low for visual requirements. Because of prismatic effect, myopes tend to wear their bifocal higher and hold their reading material lower than hyperopes, although a myope is more likely to notice and therefore complain about a segment which intrudes on his distance field.

5. Induced VERTICAL IMBALANCE found at the reading point must be corrected if it exceeds one prism diopter. This can be achieved by the use of slab-offs, dissimilar segments or prism segments.

6. Glasses should be ADJUSTED so that they are horizontal with and equidistant from the eyes. They should be fitted close to the eyes in order to increase the angular field of the bifocal and make the division line less noticeable to the patient. Pantoscopic tilt (on all but heavy myopic prescriptions) helps bring the division line under and away from the patient's distance field.

All of these "bifocal troubles" are discussed individually in other Scientific Corner articles. Copies are available upon request.

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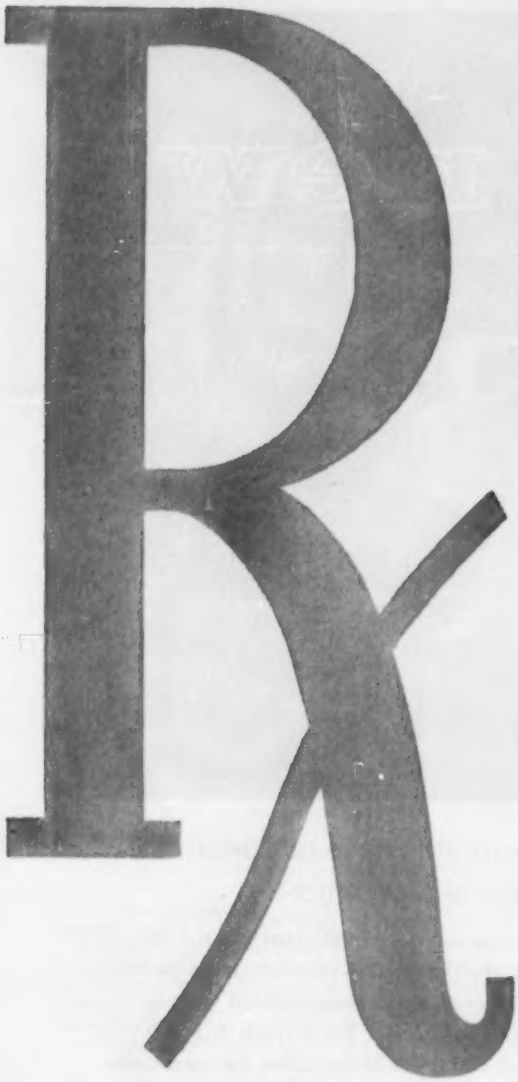

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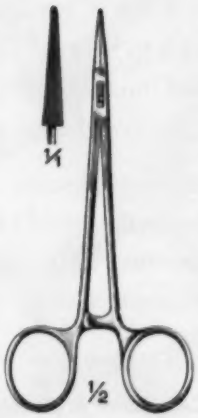

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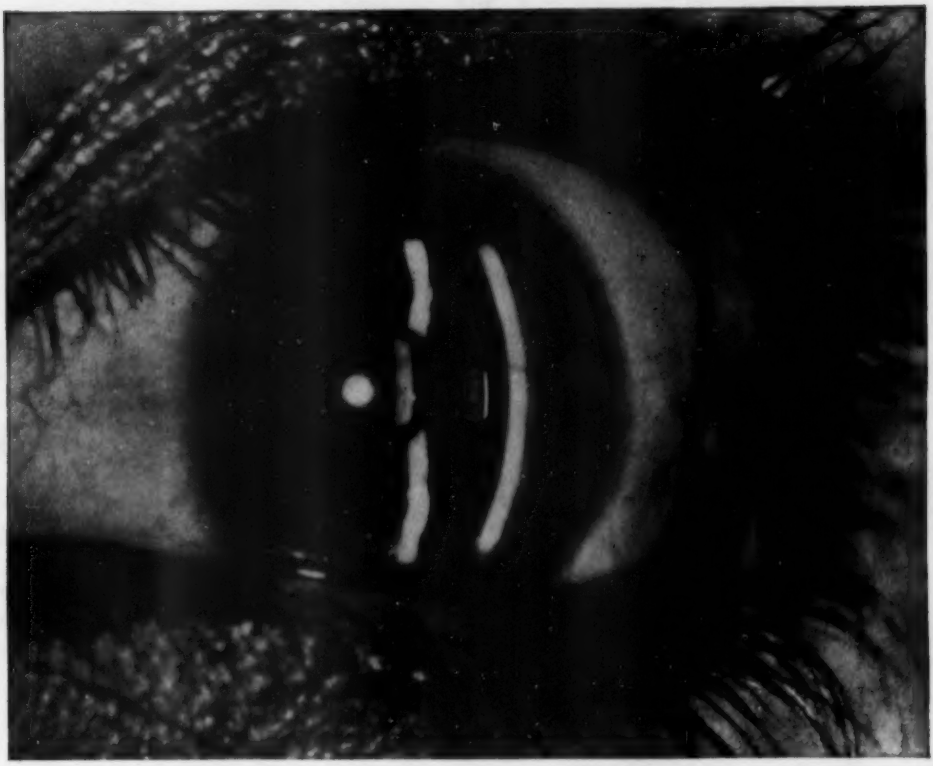

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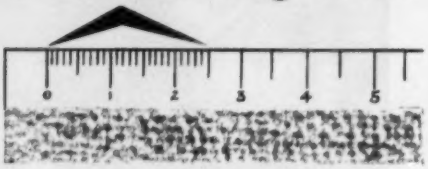

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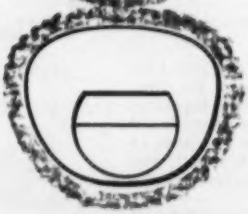

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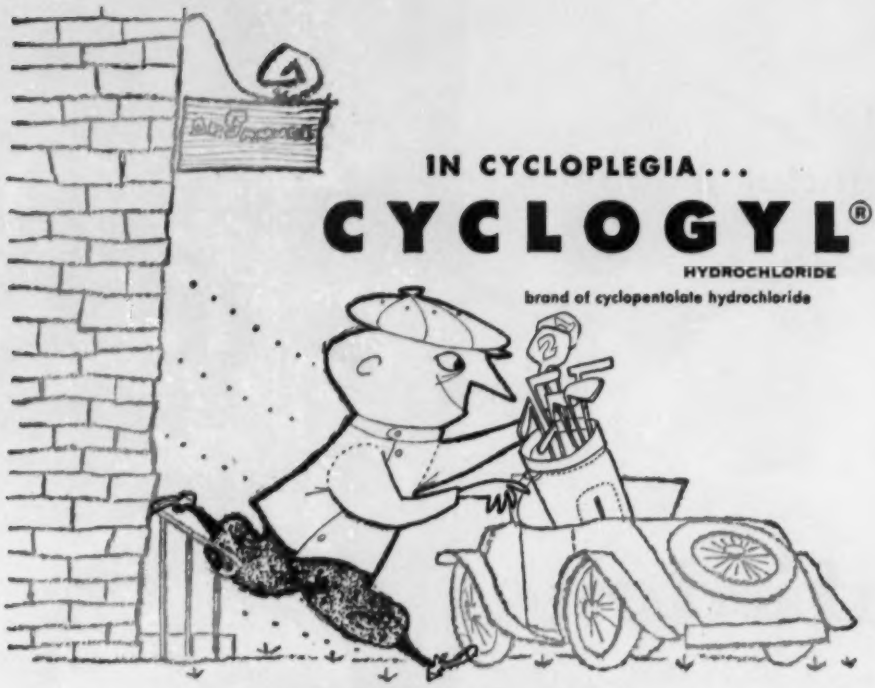

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New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1954, p. 189.

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Cyclogyl 0.5%	2	1.10	24†
Homatropine 2% or 4%	2	2.00	48

*Successive drops at five-minute intervals.

†Recovery time reduced to six hours after one-percent pilocarpine.

1. Gordon, D. M., and Ebrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

"the chief handicap of maximum cycloplegia, namely its incapacitating effect, is minimized . . ."

Getter, B. C.: A.M.A. Arch. Ophth. 51:467 (Apr.) 1954.

Cyclogyl, "by virtue of its brevity, rapidity of action, and consistent depth of cycloplegia, will be [a drug of choice] for routine refraction . . ."

Ehrlich, L. H.: New York J. Med. 53:3015 (Dec. 15) 1953.

Dosage:

Cycloplegia — One drop 1.0%, in each eye (or two drops of 0.5%) produces maximal cycloplegia in 30-60 minutes. Recovery time is normally 4-12 hours spontaneously. Pilocarpine reduces recovery time. In deeply pigmented eyes, 2 drops of 1.0% in each eye, instilled 10 minutes apart, achieves satisfactory cycloplegia in 98% of cases.

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Beta Hypophamine (Vasopressin)

Its Effect upon Intraocular Pressure and Aqueous Flow in Normal and Glaucomatous Eyes

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and
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Introduction

The antidiuretic effect produced by the vasopressor hormone of the posterior pituitary lobe—β-hypophamine; vasopressin U. S. P.—is well known.[1] It promotes the resorption of water by its action on the renal tubules.

Interest in this hormonal effect was stimulated by a desire to increase the hemodilution following water drinking as a provocative test for glaucoma. It was hoped that the more intense and uncompensated decrease of osmotic pressure of the plasma produced by the administration of vasopressin with the water might lead to more consistent changes and a higher percentage of significant rises in intraocular pressure in glaucoma suspects. Meves[2] reported that systemic Pituglandol (containing vasopressin and oxytocin) given with the water-provocative test produced a greater and more prolonged rise in ocular tension than could be obtained with water drinking alone. He also cited two patients with glaucoma who had negative water-provocative tests, but positive tests when Pituglandol was given with the water. A similarly modified water test was considered to be of importance in the diagnosis of latent glaucoma by Weinstein.[3] Leydhecker,[4] however, reported that posterior pituitary extracts failed to alter the results of the water imbibition test. It was the original purpose of this investigation to repeat Meves' work, using purified β-hypophamine (vasopressin), and to evaluate the effects induced by tonography. As a preliminary control study, vasopressin alone was administered to rabbits. Confirming the findings of Schläppi and Franceschetti,*

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* References 5-6.

vasopressin was found to lower intraocular pressure in this species when administered either locally or systemically.[7]

In order to avoid such side-effects as bradycardia, arterial hypertension, constriction of the coronary arteries with resultant myocardial ischemia, hyperperistalsis, nausea, and vomiting† topical administration was selected, rather than the systemic route, for all work in patients.

The local administration of vasopressin to one eye also offered an opportunity for evaluating its effects on the homolateral eye, separate at least in part from systemic pressor actions, and with the contralateral eye serving as a control.

Materials and Methods

For clinical trial on patients vasopressin was administered topically to one eye of a series of 75 patients. Of the total, there were 22 normal and 53 glaucoma patients. The glaucoma group included 42 with open-angle (chronic simple), 2 with angle-closure, and 9 with secondary types. Whenever possible, the contralateral eye was used as a control in each patient. Exceptions were made in cases of recent surgery on one eye.

The patient was placed in the supine position and a local anesthetic (Ophthaine [2-diethylaminoethyl-3-amino-4-propoxybenzoate], 0.1 ml.) was instilled into the cul-de-sac of both eyes. After a short interval tonometry or tonography was performed. All tonography was carried out with a Müller electronic tonometer connected to a Leeds & Northrup recorder. Following the initial measurements, 0.1 ml. of vasopressin‡ solution (20 pressor units per milliliter) was instilled into the cul-de-sac of one eye only ("homolateral eye"). Usually the eye with the higher tension was selected for such administration. The lid margins were retracted slightly from the globe for one minute following the application of the drops.

In the manual tonometry group, tensions were taken every 15 minutes on both the homolateral and the contralateral eyes for at least one hour after drug administration. The one-hour tensions were used for evaluation of the effect of vasopressin. The post-treatment tonographic determinations were made one hour after administration of the test dose, and these eyes had no measurements made in the interval. By convention, all measurements were made on right eyes first, regardless of which eye had received the vasopressin. From the tonographic tracings values for the intraocular pressure (P_o) and the facility of outflow (C) were computed, using the 1955 tables of Friedenwald.[10]

Results

Topical administration of vasopressin was found to lower intraocular pressure in almost all homolateral eyes tested, both normal and glaucomatous. This was accomplished without signs of local irritation or systemic side-effects and without significant effect on the contralateral control eye of the same patients. Typical time curves obtained by manual tonometry after vasopressin administration are presented in Figure 1 for representative normal and glaucomatous eyes. Between 15 and 45 minutes were required for the maximum pressure-lowering effect to occur. The duration of depression of intraocular pressure was variable, but was usually less than four hours.

† References 8-9.

‡ The vasopressin used in these studies was supplied as Pitressin through the courtesy of Parke, Davis & Company.

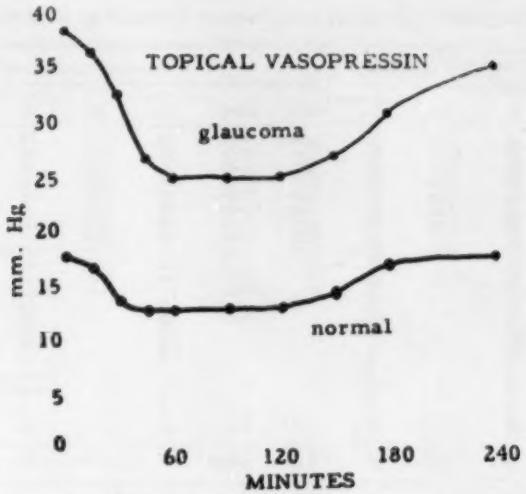

Fig. 1.—Time course of intraocular pressure following topical vasopressin in normal and glaucomatous eyes.

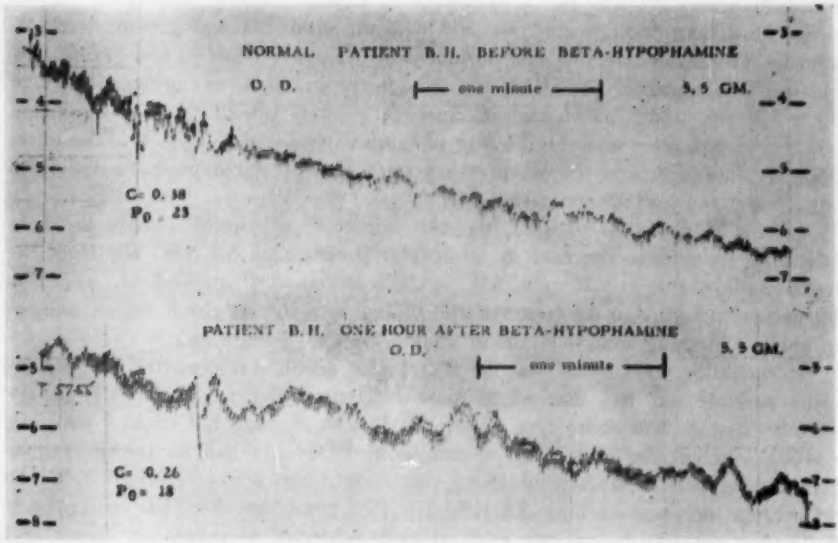

Fig. 2.—The effect of topical vasopressin on a normal eye.

In 22 normal eyes with no evidence of glaucoma, vasopressin administration resulted in a decrease in intraocular pressure of 2 to 9 mm. Hg. with an average decrease of 5.0 mm. Hg (27%) from the mean initial pressure of 18.3 mm. Hg. The effect on the contralateral, untreated eyes of 18 patients varied from a decrease of 3 mm. Hg to an increase of 3 mm. Hg, with an insignificant average decrease of 0.7 mm. Hg (4%) from the mean initial pressure of 17.0 mm. Hg (Table 1).

Repeated tonograms before and after vasopressin revealed that the fall in

TABLE 1.—*Effect of Topical Vasopressin on Normal Eyes (22 Patients)*

Patient	Homolateral Eye* (Vasopressin)					Contralateral Eye* (Control)				
	P_1	C_1	P_2	C_2	$\Delta F\%$	P_1	C_1	P_2	C_2	$\Delta F\%$
1	23	0.38	18	0.26	−58	19	0.24	18	0.28	+ 4
2	21	0.41	16	0.41	−55	17	0.40	18	0.40	+14
3	20	0.27	17	0.17	−56	17	0.20	18	0.23	+15
4	20	0.24	16	0.17	−58	18	0.25	18	0.22	−12
5	20	0.26	15	0.16	−69	17	0.25	17	0.20	−20
6	19	0.28	15	0.20	−60	17	0.30	17	0.27	−10
7	19	0.30	16	0.20	−56	18	0.33	21	0.25	− 5
8	17	0.35	14	0.22	−64	16	0.32	17	0.30	+ 9
9	23	0.32	17	0.20	−66			Prosthesis		
10	21	------	12	------		21	------	18	------	
11	21	------	13	------		19	------	17	------	
12	19	------	13	------				Surgery		
13	19	------	15	------		19	------	18	------	
14	18	------	13	------		13	------	13	------	
15	17	------	10	------		15	------	13	------	
16	17	------	13	------		16	------	16	------	
17	15	------	9	------		17	------	16	------	
18	13	------	8	------				Surgery		
19	13	------	7	------				Surgery		
20	12	------	7	------		12	------	11	------	
21	19	------	14	------		19	------	18	------	
22	17	------	15	------		16	------	16	------	
Mean ± S.D.	18.3	0.31	13.3	0.22	−60±5	17	0.29	16.7	0.27	−1±12

*P_1=intraocular pressure before vasopressin; C_1, facility of outflow before vasopressin; P_2, intraocular pressure one hour after vasopressin (to homolateral eye only); C_2, facility of outflow one hour after vasopressin (to homolateral eye only); $\Delta F\%$, per cent change in aqueous flow (assuming Pv=10 mm. Hg and is not altered). t=12 ($\Delta F\%$ vasopressin re. control)

intraocular pressure was not associated with improvement in facility of outflow (Fig. 2). These findings are consistent with the thesis that vasopressin decreases aqueous production. In the nine normal patients, where repeated tonograms were obtained, vasopressin produced an average suppression of aqueous flow of $60 \pm 5\%$ (assuming no change in episcleral venous pressure). No significant changes in flow were noted in the control, contralateral eyes (Table 1). The effect upon the rate of flow in the vasopressin-treated eyes proved statistically significant when compared with the control eyes.

In the 53 glaucoma patients, the eyes subjected to topical vasopressin demonstrated an average decrease in intraocular pressure of 6.3 mm. Hg from the mean initial value of 32 mm. Hg, a 20% decrease (Tables 2, 3, 4). The intraocular pressure in the contralateral, control eyes in this group fell an average of only 1.1 mm. Hg from the mean of 26 mm. Hg (a 4% decrease).

It should be emphasized that the decrease in intraocular pressure in the glaucoma patients was less marked in those receiving other medication. Thus, the 17 untreated glaucomatous eyes (Table 2) had an average fall of 11.5 mm. Hg (34%), whereas the 18 eyes on miotics alone (Table 3) had an average fall of 5.1 mm. Hg (18%), and in the 18 eyes on miotics plus acetazoleamide (Table 4) an average decrease of only 3.1 mm. Hg (9%) was noted. Thus, vasopressin did lower intraocular pressure even in eyes subjected to maximum miotic and acetazoleamide therapy, but not as dramatically as in untreated glaucomatous eyes.

Careful tonographic studies were available on eyes from each of these groups. In 13 patients with untreated glaucoma, vasopressin administration resulted in an average suppression of aqueous flow of $59 \pm 7\%$, as compared with an insignificant increase of $1 \pm 8\%$ in the contralateral, control eyes (Table 2). Tonographic data on 13 patients under the influence of topical miotics are presented in Table 3. The homolateral eyes exhibited an average of $39 \pm 12\%$ suppression of aqueous flow, whereas the contralateral, control eyes failed to demonstrate

TABLE 2.—*Effect of Topical Vasopressin on Untreated Glaucoma (17 Patients)*

Patient	Homolateral Eye*					Contralateral Eye*				
			(Vasopressin)					(Control)		
	P_1	C_1	P_2	C_2	$\Delta F\%$	P_1	C_1	P_2	C_2	$\Delta F\%$
Open-Angle										
23	35	0.08	35	0.04	−72	38	0.15	36	0.18	+11
24	38	0.20	22	0.14	−70	35	0.30	28	0.30	+ 8
25	33	0.12	22	0.08	−66	22	0.13	17	0.22	− 1
26	24	0.20	10	0.12	−61	24	0.27	23	0.30	+ 3
27	19	0.14	13	0.15	−64	19	0.15	17	0.21	+ 9
28	35	0.08	25	0.06	−55	33	0.10	30	0.11	− 4
29	44	0.07	30	0.05	−58	40	0.08	38	0.08	− 7
30	39	0.12	24	0.10	−60	33	0.15	39	0.12	− 5
31	48	0.05	30	0.05	−47	39	0.09	36	0.09	−10
32	30	0.15	21	0.12	−60	33	0.12	30	0.15	+ 9
33	36	0.12	24	0.09	−60	30	0.17	29	0.20	+12
34	30		17			30		26		
35	32		17			29		27		
36	25		16			27		25		
37	36		25			30		28		
Narrow-Angle										
38	14	0.31	12	0.29	−53	15	0.40	15	0.40	0
Secondary										
39	39	0.07	25	0.07	−46	37	0.08	33	0.08	−15
Mean ± S.D.	33.9		22.4		−50±7	30.2		28.1		+ 1±8

*P_1=intraocular pressure before vasopressin; C_1, facility of outflow before vasopressin; P_2, intraocular pressure one hour after vasopressin (to homolateral eye only); C_2, facility of outflow one hour after vasopressin (to homolateral eye only); $\Delta F\%$, per cent change in aqueous flow (assuming Pv=10 mm. Hg and is not altered). t=20 ($\Delta F\%$ vasopressin *vs.* control)

TABLE 3.—*Effect of Topical Vasopressin on Glaucoma Under Treatment with Miotics (18 Patients)*

Patient	Homolateral Eye*					Contralateral Eye*				
			(Vasopressin)					(Control)		
	P_1	C_1	P_2	C_2	$\Delta F\%$	P_1	C_1	P_2	C_2	$\Delta F\%$
Open-Angle										
40	50	0.08	46	0.07	−21	48	0.08	44	0.09	+ 4
41	41	0.08	30	0.05	−41	16	0.19	15	0.19	−17
42	39	0.16	33	0.15	−26	36	0.19	36	0.19	0
43	37	0.09	36	0.07	−25	27	0.20	25	0.21	− 4
44	27	0.15	21	0.12	−48	23	0.29	22	0.25	−20
45	22	0.10	16	0.11	−45	21	0.06	22	0.07	+27
46	19	0.19	16	0.16	−44	20	0.24	19	0.27	+ 1
47	18	0.28	15	0.32	−29	17	0.28	17	0.28	0
48	18	0.20	17	0.17	−26	17	0.34	17	0.34	0
49	15	0.31	13	0.30	−42	15	0.31	17	0.25	+13
50	35	0.19	29	0.12	−52	22	0.24	24	0.21	+ 2
51	25	0.27	17	0.20	−65	20	0.25	22	0.21	+ 1
52	27		21			22		21		
53	24		15			24		24		
54	22		16			19		19		
Secondary										
55	20	0.10	14	0.15	−40	14	0.07	13	0.10	+ 7
56	40		34					Prosthesis		
57	19		12			19		15		
Mean ± S.D.	27.7		22.6		−39±12	22.4		21.9		− 1±11

*P_1=intraocular pressure before vasopressin; C_1, facility of outflow before vasopressin; P_2, intraocular pressure one hour after vasopressin (to homolateral eye only); C_2, facility of outflow one hour after vasopressin (to homolateral eye only); $\Delta F\%$, per cent change in aqueous flow (assuming Pv=10 mm. Hg and is not altered). t=8 ($\Delta F\%$ vasopressin *vs.* control); t=5 ($\Delta F\%$ vasopressin-miotics *vs.* vasopressin-untreated).

significant changes. Similar studies on nine patients subjected to systemic acetazoleamide and local miotics are summarized in Table 4. Vasopressin induced further decreases in aqueous secretion, averaging 24 ± 10%, with little change in the control eyes. In each of these glaucoma groups, the alterations in flow in the eye subjected to topical vasopressin are based upon the assumption of no alteration in episcleral venous pressure and are statistically significant as compared with those in the control eyes. Furthermore, the differences in effect of vasopressin on untreated glaucomatous eyes as compared with that on glaucomatous eyes treated with miotics and acetazoleamide are statistically significant.

TABLE 4.—*Effect of Topical Vasopressin on Glaucoma Under Treatment with Miotics and Acetazoleamide (18 Patients)*

Patient	Homolateral Eye* (Vasopressin)					Contralateral Eye* (Control)				
	P_1	C_1	P_2	C_2	$\Delta F\%$	P_1	C_1	P_2	C_2	$\Delta F\%$
Open-Angle										
58	39	0.12	28	0.16	−17	39	0.11	30	0.17	+10
59	34	0.19	30	0.21	− 8	25	0.21	25	0.24	+13
60	25	0.20	22	0.19	−24	27	0.20	27	0.22	+10
61	23	0.12	20	0.10	−36	20	0.10	20	0.09	−10
62	22	0.19	20	0.15	−34	19	0.12	20	0.10	− 8
63	20	0.24	19	0.22	−18	18	0.20	18	0.20	0
64	30	0.10	28	0.10	−10	19	0.17	17	0.23	+ 5
65	42		39			20		20		
66	33		30			30		29		
67	29		24			29		27		
68	24		21			19		19		
69	19		15			17		15		
Chronic narrow-angle										
70	29	0.10	24	0.09	−34	25	0.20	27	0.18	+ 2
Secondary										
71	22	0.10	19	0.09	−32	15	0.13	15	0.12	− 8
72	78		71			22		22		
73	65		65			10		10		
74	44		44			22		22		
75	29		30			59		59		
Mean ± S.D.	33.7		30.6		−24±10	24.2		23.4		+2±8

*P_1=intraocular pressure before vasopressin; C_1, facility of outflow before vasopressin; P_2, intraocular pressure one hour after vasopressin (to homolateral eye only); C_2, facility of outflow one hour after vasopressin (to homolateral eye only); $\Delta F\%$, per cent change in aqueous flow (assuming Pv=10 mm. Hg and is not altered). *t*=5 ($\Delta F\%$ vasopressin *vs.* control); *t*=8 ($\Delta F\%$ vasopressin-miotics-acetazoleamide *vs.* vasopressin-untreated); *t*=3 ($\Delta F\%$ vasopressin-miotics acetazoleamide *vs.* vasopressin-miotics).

Comment

It is apparent that topically administered vasopressin decreased aqueous flow in the normal and untreated glaucomatous eyes of this series by some 60%. This resulted in a fall in intraocular pressure of variable amount. Associated with its administration was a significant decrease in facility of aqueous outflow in many eyes. Similar alterations in facility have been observed in normal rabbit eyes following administration of this hormone,[7] as well as in rabbit and normal human eyes subjected to systemic carbonic anhydrase inhibitors.§ It is not possible to determine from the present data whether vasopressin acted directly on the outflow mechanism in such eyes or whether the changes in facility observed were a compensatory device for maintaining intraocular pressure in spite of depressed secretion. It is of interest that the decrease in facility following vasopressin administration was not prevented by miotic administration (occurring in 16 of the 22 miotic-treated eyes versus 18 of 22 eyes not subjected to miotics). The finding that vasopressin was less effective in reducing intraocular pressure and flow in glaucomatous eyes under treatment with miotics or miotics plus acetazoleamide needs confirmation and further study. On the one hand, it is noteworthy that vasopressin further suppressed the residual aqueous secretion following carbonic anhydrase inhibition. On the other hand, the less effective response to vasopressin of miotic-treated glaucomatous eyes than of normal eyes or untreated glaucomatous eyes requires explanation. One suggestion is the possible antagonism of the vasodilating effects of miotics in partially overcoming or preventing the vasoconstrictive action of vasopressin.

The relationship of posterior pituitary function and intraocular pressure has been commented upon by several authors.‖ Zondek and Wolfsohn[15] have de-

§ References 11-12.

‖ References 13-14.

scribed a primary glaucoma associated with pituitary dysfunction and called it "pituitary-diencephalic glaucoma." Patients with juvenile glaucoma and signs of hypopituitarism have been reported to have their intraocular pressures normalized by the administration of posterior lobe extracts of the pituitary.[16] Ballintine ¶ has postulated that the inhibition of circulating, endogenous antidiuretic hormone resulting from water drinking might be the mechanism of the induced rise in intraocular pressure. All of these suggestions would fit well with the possibility of endogenous vasopressin as a hormonal regulator of aqueous secretion. Tonographic studies in patients with diabetes insipidus would be of great interest in this regard.

It should be emphasized, however, that the doses of vasopressin (2 units) used in these studies are of a much higher order of magnitude than the level of circulating antidiuretic hormone and are much closer to vasoconstrictor doses. Colle, Duke-Elder, and Duke-Elder [17] noted prolonged vasoconstriction of intraocular vessels in intact anesthetized dogs and perfused heads of dogs following the systemic administration of pituitary posterior U. S. P. (3-5 units). Recently, Wudka and Leopold [18] have observed the vessels of the rabbit uvea through a plastic window in the proptosed eye. They reported that local, as well as systemic, administration of vasopressin produced marked vasoconstriction of the ciliary arterioles. Such a decrease in ciliary blood supply in rabbits provides an attractive explanation for the decreased production of aqueous humor observed in this species.

The major arterial circle of the iris can be observed directly in the undisturbed eye of the albino rabbit. This vessel is fed directly by the ciliary arteries and may be studied under slit-lamp magnification. Topical vasopressin resulted in a marked constriction of these vessels, to the point of disappearance of the blood column. The time course of the vasoconstriction was noted to be strikingly similar to the induced ocular hypotension in such rabbit eyes.[7] These findings offer suggestive support for a vascular basis for the vasopressin suppression of secretion in the rabbit. On repeated administration of topical vasopressin, rabbits became resistant to its pressure-lowering effects. Such rabbits did not exhibit either the vasoconstriction of the iris vessels or the secretory suppression in response to vasopressin. Following a rest period of 12-24 hours, these eyes became responsive once again.

Whether constriction of ciliary arteries occurs in human eyes following vasopressin is a matter of conjecture. It is interesting to speculate that this drug may be the medical counterpart of cycloanematization of the ciliary body, decreasing its blood supply and partially suppressing aqueous humor formation. It is, nevertheless, of clinical interest to confirm the findings of Schläppi and Franceschetti # that vasopressin is capable of lowering intraocular pressure in normal and glaucomatous human eyes.

The role of vasopressin in the therapy of the glaucomas is in need of further study. The short-term topical administration of this agent has already proved of value in lowering intraocular pressure. However, attempts at long-term treatment have been uniformlly discouraging. In 10 patients treated thus far, repeated topical vasopressin administration led rapidly to an unresponsive state, much as in the studies on rabbit eyes. The antagonism of miotics and

¶ Ballintine E. J.: Personal communication to the authors.

References 5-6.

vasopressin presented an additional obstacle to the use of this agent in glaucoma therapy. However, even those patients with open-angle glaucoma treated with vasopressin alone rapidly became resistant to its effects on intraocular pressure following the initial dramatic response. In each instance it was necessary to discontinue vasopressin therapy and institute conventional treatment. The nature of the resistant state to vasopressin requires further investigation. Since it occurs in rabbits, opportunities are offered for an experimental approach to its mechanism.

Summary

The antidiuretic hormone, β-hypophamine (vasopressin), lowers intraocular pressure when applied topically to normal and glaucomatous human eyes.

Repeated tonography reveals that the fall in intraocular pressure results from an average (mean ± S. D.) suppression of aqueous flow of 60 ± 5% in normal eyes and 59±7% in untreated glaucomatous eyes.

Glaucomatous eyes receiving miotic therapy appear to respond less dramatically to vasopressin administration (39 ± 12% suppression of flow), and those eyes subjected to miotic and acetazoleamide therapy demonstrate even less (24 ± 10%) decrease of aqueous flow.

The clinical usefulness of vasopressin appears to be limited to short-term application because of the rapid development of a resistant state of the eye to the pressure-lowering effects of the drug.

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Studies on Aqueous Passages in the Eye of the Rabbit

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It is the purpose of this paper to report observations on aqueous veins and on other possible aqueous passages in normal and pathological rabbit eyes.

Method

Kleinert (1953) applied an ingenious technique for the demonstration of aqueous veins in human eyes by the injection into the anterior chamber of 0.1% fluorescein in isotonic saline. The stained aqueous humor is then observed in darkness by means of ultraviolet light, which makes it stand out selectively against an almost entirely dark background. This method was used in our experiments. For low magnifications (loupe), a fluorescent lamp, which yields ultraviolet light only, proved to be satisfactory. For higher magnifications a slit lamp was used with a dark violet gelatin filter placed in the beam.

The studies were done on chinchilla rabbits and albino rabbits (3 kg. or more), which were first subjected to tonometry. Their heads and legs were immobilized, and 0.5% tetracaine (Pontocaine) hydrochloride was instilled in the conjunctival sac, following which the tension was taken. Pentobarbital (Nembutal) sodium was injected peritoneally to produce deep narcosis for five to six hours. Since it is important to prevent unnecessary manipulations on the eye which may cause congestion of conjunctival vessles, the nictiating membranes were removed several weeks previously and no sutures or specula were used. In order to prevent interference with the systemic blood circulation which might cause congestion of the cranial vessels, bandages and restraint boxes were omitted and the head of the animal was kept in the same level as the body at all times.

About an hour after the injection of pentobarbital sodium the intraocular pressure was taken again, and a drop from 3 to 7 mm. Hg was found. This phenomenon was described by Stone and Prijot (1955) and is in our opinion due to the relaxation of the extraocular muscles and to a depression of the blood pressure.

For the injection of fluorescein a 26-gauge needle was passed through the anterior layers of the cornea 2 mm. inside the limbus. It was pushed 4 mm. toward the corneal center and then passed through the remaining deep layers to enter the anterior chamber.

About 0.2 cc. of fluorescein was injected under moderate pressure. The needle was then withdrawn by a fast movement, while the pressure on the piston was maintained. This way it is possible to obtain an intraocular pressure of 20 to 40 mm. Hg and to prevent loss of aqueous, since the tiny wound closes like

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a valve. Immediately after the injection the pressure was taken again. If fluorescein was spilled, the conjunctival sac was flushed with saline solution at body temperature. When aqueous was lost during the injection, the eye was not used for these experiments.

Results

A. The Morphology of Chamber Angle and Aqueous Veins

(Six Chinchilla Rabbits with 12 Normal Eyes)

Under ultraviolet illumination the stained aqueous, which can be seen through the cornea, exhibits a brilliant yellowish-green color. The part of the anterior chamber which lies behind the scleral part of the limbus shows up as a less luminous circular area which extends 2.5 mm. beyond the pigmentation of the corneoscleral junction (Fig. 1).

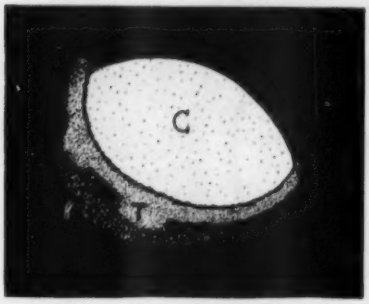

Fig. 1.—The appearance of the anterior segment of the rabbit eye after injection of fluorescein into the anterior chamber and observation by ultraviolet light. *C*, cornea; *T*, tongue-like extensions from the chamber angle. The part of the anterior chamber which lies behind the sclera is less luminous than the part behind the cornea.

A few minutes after the injection of fluorescein tongue-like extensions from the chamber angle appeared (Fig. 1, *T*). They were about 3 mm. long and 5 mm. wide and at the beginning of the examination had very distinct outlines, which became increasingly blurred by diffusion of fluorescein after 15 minutes. They were present in 9 of the 12 eyes examined and ranged in number from one to four.

In each eye 5 to 11 aqueous veins were found which originated with a little loop immediately at the limbal pigmentation or within a distance of 2 mm. from it. In a few instances they seemed to originate from the tongue-like extensions from the angle of the anterior chamber. They had diameters from 0.25 to 1.0 mm. and lengths from 2 to 13 mm. Many first ran parallel to the limbus and then turned radially to enter a recipient vessel, where they produced stratification and finally mixed with the blood. This caused an abrupt disappearance of the fluorescent streak (Fig. 2).

B. The Influence of the Intraocular Pressure on the Visualization of the Aqueous Passages

If the intraocular pressure was lower after injection of fluorescein than it was before narcosis, no aqueous veins were observed. If the intraocular pressure was the same as before narcosis or was higher, all aqueous veins could be visualized. Fine anastomoses between the main aqueous veins filled with stained aqueous and became evident when the intraocular pressure was over 40 mm. Hg (Fig. 3). They disappeared after the pressure returned to the initial value. Simultaneously with the rise in tension the fluorescent streak in the aqueous veins became wider.

C. The Influence of the Episcleral Venous Pressure on the Visualization of the Aqueous Passages

When the jugular veins were compressed, the conjunctival vessels showed a gradual increase in their blood content and the aqueous veins appeared shorter

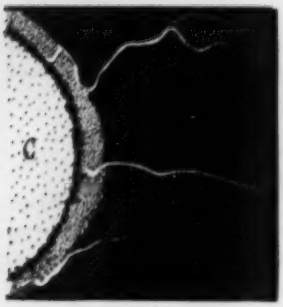

Fig. 2.—Three aqueous veins originate at the limbus and have become visible after injection of fluorescein into the anterior chamber and observation by ultraviolet light. Intraocular pressure 19 mm. Hg. *C*, cornea.

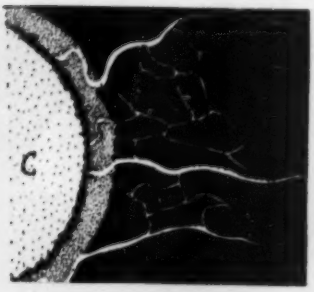

Fig. 3.—The same area as in Figure 2. The intraocular pressure rose to 50 mm. Hg after the globe was compressed. A network of fine anastomoses between the main aqueous veins filled with stained aqueous. *C*, cornea.

and less conspicuous and sometimes even disappeared. If pressure was exerted on the globe, the aqueous veins reappeared in their initial width and length.

An impressive accident occurred when one of the rabbits died during the experiment, obviously from an overdose of pentobarbital sodium shortly after the injection of fluorescein into the anterior chamber. The aqueous veins became longer after the heart beat had stopped, and when pressure was exerted on the globe the vascular bed of the episclera and conjunctiva filled with stained aqueous.

D. The Glass-Rod Test in the Rabbit Eye

In the majority of the aqueous veins examined the glass-rod test was positive. If the episcleral venous pressure was increased by compressing the jugular veins for a few minutes, a negative glass-rod test was obtained.

E. The Aqueous Passages After Puncture of the Anterior Chamber

The anterior chambers of two rabbit eyes were punctured, and the aqueous was withdrawn. After 15 minutes they became refilled with a protein-enriched secondary aqueous which contained several fibrin clots. In one eye the intraocular pressure went up to 68 mm. Hg, and in the other, to 90 mm. Hg for about three hours. No aqueous veins could be visualized after the injection of fluorescein, and the tongue-like extensions from the chamber angle were also absent.

Another animal was given 5000 units of heparin every 12 hours intramuscularly three days before the anterior chamber was emptied in order to prevent the secondary aqueous from clotting (Binder and Binder, 1953). In these two eyes the rise in intraocular pressure was moderate and did not exceed 10 mm. Hg. After the injection of fluorescein into the anterior chamber the tongue-like extensions from the chamber angle were visible. However, only one aqueous vein was seen in one eye and none in the other.

F. The Aqueous Passages in Secondary Glaucoma

No aqueous veins or tongue-like extensions from the chamber angle were

demonstrated by injection of fluorescein into the anterior chamber in two glaucomatous rabbit eyes, which had an intraocular pressure of 90 mm. Hg. The glaucoma was secondary to an anterior uveitis which followed exogenous infections a year previously.*

G. The Aqueous Passages in a Phthisical Eye

The attempt to perform a lens extraction in a rabbit eye eight months previously had resulted in considerable loss of vitreous, and the eye had become phthisical, with marked deformation and reduction of the corneal diameter to 8 mm. The other eye, which was normal, had a corneal diameter of 14 mm. The globe was hypotonic, and the injection of fluorescein into the anterior chamber did not result in demonstration of aqueous veins, nor were the tongue-like extensions from the chamber angle visualized.

H. The Aqueous Passages After Iridencleisis

Iridencleisis had been performed in three normal rabbit eyes eight months previously. Injection of fluorescein into the anterior chamber showed the aqueous veins and the tongue-like extensions as in normal rabbit eyes. In one eye a faint luminous area was seen in the scar, probably corresponding to some filtration of aqueous. No such evidence was found in the other two eyes.

I. The Aqueous Passages After Cyclodialysis

In the eye of an albino rabbit which had been cyclodialyzed 10 months previously, a faint but definite streak of fluorescence was observed in the area of the surgical procedure shortly after the injection of fluorescein into the anterior chamber. After compression this fluorescent area became more conspicuous and

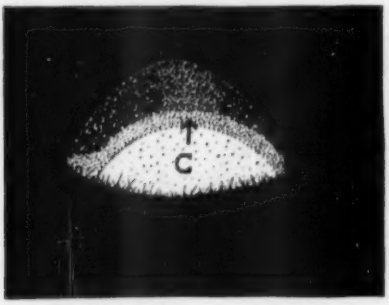

Fig. 4.—Anterior segment of a rabbit eye 10 months after cyclodialysis. After injection of fluorescein into the anterior chamber and observation by ultraviolet light some filtration of aqueous was visible in the area of the surgical procedure (arrow). *C*, cornea.

enlarged considerably within the next 10 minutes (Fig. 4). In the same eye, three aqueous veins and one tongue-like extension from the chamber angle were seen.

Comment

Careful descriptions of aqueous veins in the rabbit eye were given first by Weekers and Prijot (1950), later by Greaves and Perkins (1951), and then by Wegner and Intlekofer (1952). These authors agree that aqueous veins are a constant finding and have the same appearance as those found in human eyes.

Weekers and Prijot destroyed the aqueous veins and observed thereafter a short period of hypertension followed by a lasting hypotony. They concluded that, in addition to the aqueous veins, there might be other passages for the elimination of the aqueous humor.

* The rabbits mentioned under F, G, H, and I had been used for the surgical training the residents receive in our department.

The tongue-like extensions from the chamber angle described above are probably passages for the transport of aqueous humor to the uvea, where it may be absorbed. These extensions seem to be portions of the "cilioscleral sinus" described by Troncoso (1942), which have been infiltrated by stained aqueous.

Kleinert (1953) saw similar extensions after iridencleisis in glaucomatous human eyes, which he interpreted as intrascleral reservoirs of aqueous humor.

The failure to demonstrate aqueous veins and tongue-like extensions from pressure seems to indicate that the "safety-valve" theory of Thomassen (1949) also applies in the case of the rabbit eye.

Zwiauer and Bornschein (1951) proved that the rise in intraocular pressure following the removal of the primary aqueous is caused by fibrin in the secondary aqueous, which blocks the chamber angle. Although heparin would prevent the formation of fibrin, it appears from the findings described above (E) that the secondary aqueous is still too viscous to pass through the structures of the angle region. This would explain the moderate rise in intraocular pressure and the reduced visualization of the aqueous veins after injection of fluorescein into the anterior chamber.

The failure to demonstrate aqueous veins and tongue-like extensions from the chamber angle in the two glaucomatous rabbit eyes (F) and in the phthisical eye (G) may be attributed to structural changes in the angle region secondary to the long-standing conditions.

Summary and Conclusions

By injection of fluorescein into the anterior chambers and observation by ultraviolet light, the aqueous veins and tongue-like extensions from the angle of the anterior chamber were observed in rabbit eyes. These tongue-like extensions are believed to be evidence of the cilioscleral sinus (Troncoso, 1942) and may serve as aqueous passages to the uvea.

The responses of the aqueous veins to the intraocular pressure and the episcleral venous pressure were found to be similar to the responses in the human eye.

No aqueous veins or tongue-like extensions from the chamber angle could be visualized in two glaucomatous eyes and in one phthisical eye.

The aquous passages after iridencleisis and cyclodialysis in rabbit eyes were studied.

It is felt that the observations recorded in this paper indicate transport of aqueous humor to the uvea. More work, however, is necessary to clarify this assumption.

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Angiomatosis Retinae

Report of a Case with Histologic Examination

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During the past two decades reports in the United States and Europe have been unanimous that the best treatment of angiomatosis retinae is diathermy coagulation of the classic "bee's nest" lesion and the vessels extending to it. If the angiomatous lesion is early in development, localized, and located peripherally, the prognosis for useful vision is good, though there is always the possibility of cerebellar involvement. In 1943 Cordes and Dickson reported favorable results with x-ray irradiation, but during the intervening years these authors have come to prefer diathermy coagulation. In 1943 Guyton used coagulation diathermy upon both eyes of a 13-year-old girl. The early lesion eye retained normal vision, and the late lesion eye was retained, though it did not regain vision. Eight years later the process extended into the cerebellum and the patient died.

In 1948 Lewis reported two patients whom he had treated with diathermy and had followed for five and one-half and three years, respectively. The first case was advanced, and, though the angioma and large vessels were destroyed and the eyeball was preserved, vision was not restored. In the second patient the lesion was an early one and normal vision was still present after 32 months. Now, 8 years later (a total of 11 years of observation) Lewis states that the vision is still normal in the early case.

In 1951 Lloyd reported a case in a 16-year-old girl whom he had been following for eight years. She had a tremendous enlargement of both main temporal arteries and veins, in which a "bee's nest" finally formed. The process became bilateral, then extended into the cerebellum, formed a cyst, and caused complete blindness.

In 1952 Guillaumat and Mercier, after trying cortisone therapy and finding it of no value, successfully coagulated an early "bee's nest" lesion. The eye retained good vision, though the retina was destroyed lateral to the lesion. In two other eyes the macula was destroyed by diathermy and considerable pigmentary changes resulted. In three other eyes this condition was found to be too far advanced for diathermy coagulation.

The well known polymorphism of angiomatosis often makes its recognition difficult. Although the usual clinical course begins with vascular dilation and angiomatous formation, hemorrhages and exudates soon appear. This is followed by massive exudation and retinal detachment, with eventual secondary glaucoma and destruction of the eye. However, it is not unusual for the process to begin centrally within the eye, with secondary glaucoma ensuing immediately.

Report of Case

A girl, aged 14, the fifth in a family of eight girls and two boys, complained of poor vision and occasional pain in her left eye. Both parents had 20/20 vision in each eye and healthy fundi.

When the girl was first examined, in November, 1948, the right eye was normal

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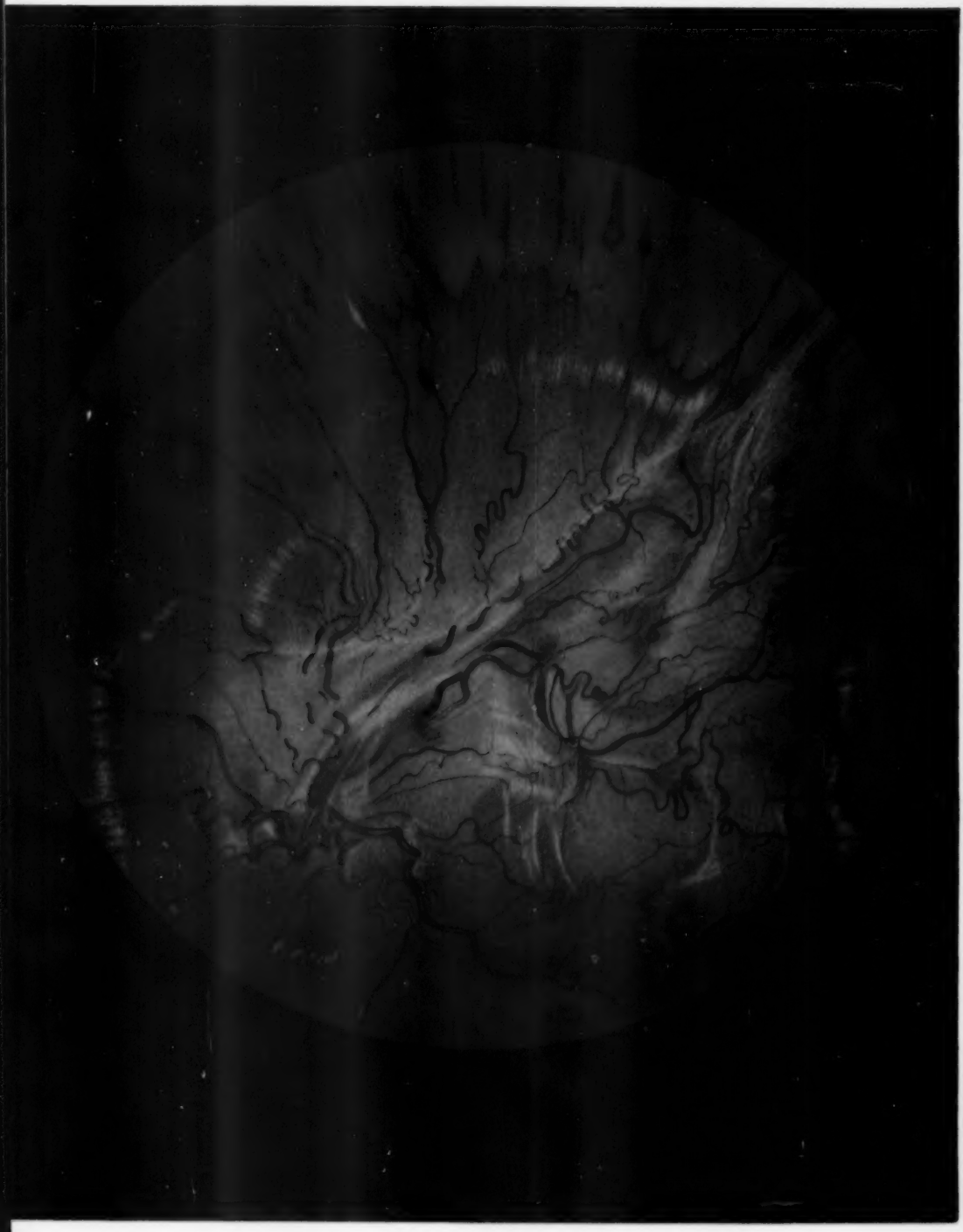

Fig. 1.—Fundus painting. (The painting is by Mrs. Mary Nicholl Burnham.)

except for a suggestion of tortuosity of the retinal vessels. The right visual field was normal. Externally, the left eye appeared normal. The left vision was 6/200; the ocular tension, 30 mm. Hg (Schiøtz). The media of the left eye were clear. Fundus study showed (Fig. 1) that the disc was not well demarcated and that the vessels extending from the region of the disc over the elevated lesion were dilated, segmented, and tortuous. The main lesion was moderately elevated and extended in roughly quadrilateral form into the upper nasal quadrant. Each border of the lesion was about 4 disc diameters in length. It was difficult to decide whether the lesion was a detachment of the retina with edema and exudates from angiomatosis or whether a tumor mass was present. The lesion extended below the macula, but in the other three quadrants of the eye the structures appeared within normal limits. (One consultant recommended immediate enucleation for neoplasm.) The possibility of an associated arteriovenous-aneurysm of the retina and midbrain was considered, but carotid arteriograms were unsuccessful in demonstrating this.

An enucleation was recommended, but it was declined by the patient and her mother.

A year later, the vision of the left eye had decreased to light perception. The ocular tension was 30 mm. Hg (Schiøtz), despite miotics in strong concentrations. Pain in the left eye had increased. The fundus study showed that the lesion had encroached further upon the optic disc and had extended further temporally. The upper temporal edge had become irregular and pigmented, and it seemed to be larger. The right eye was healthy, and its vision was 20/20. There were no evidences of involvement of vascular abnormality in the cerebellum, kidneys, or elsewhere in the body.

In January, 1950, an enucleation was performed (a Stone-Jardin implant was sutured in Tenon's capsule), and the sections were interpreted by Dr. J. S. Friedenwald:

"The retina is markedly edematous and of irregular thickness. Cystic edema involves all layers of the retina, but is more marked in the deeper layers with

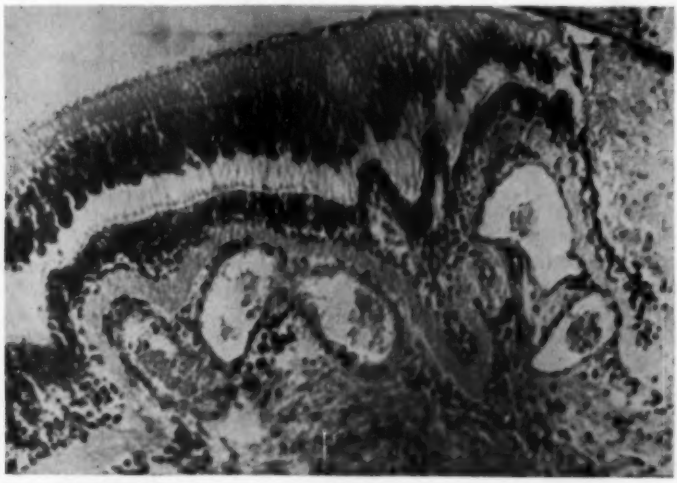

Fig. 2.—Cystic edema involves all retinal layers, more marked in the deeper layers, with capillary distortion in the outer nuclear and outer plexiform layers.

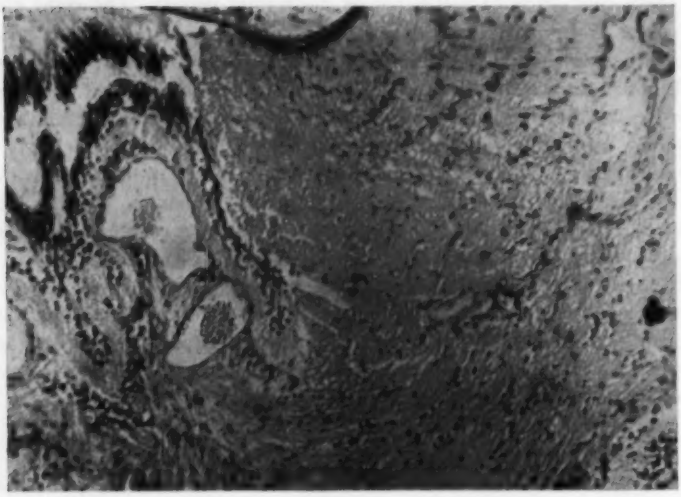

Fig. 3.—The optic nerve shows edema of the nerve fiber layer at the margin of the nerve head and enlarged vessels.

marked distortion of the capillaries present in the outer nuclear and outer plexiform layers, and an occasional dilated vessel can be seen in this region (Fig. 2). One large blue-staining deposit is seen in the rods and cones layer in one section, probably representing amyloid degeneration of the retina. The superficial retinal vessels are dilated. Only half of the optic nerve appears in the section, but it is normal except for edema of the nerve fiber layer at the margin of the nerve head and enlarged vessels (Fig. 3).

"Impression: angiomatosis retinae."

The patient has been examined several times a year since 1950, the last examination being made in March, 1956. The right vision remains 20/20; the peripheral field extends normally; the blind spot is normal in size, and the retinal vessels show the same slight tortuosity. The patient is now 21 years old. There is no evidence of extension of the angiomatous dilation elsewhere in the body.

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Experimental Tonography

II. The Effects of Vasopressin, Chlorpromazine, and Phentolamine Methanesulfonate

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The establishment of the relative validity of tonography on rabbit eyes has permitted an evaluation of the partial suppression of aqueous secretion by acetazoleamide.* In addition to acetazoleamide, three compounds have been observed by tonometry to lower intraocular pressure in rabbits.† These compounds are vasopressin (β-hypophamine; Pitressin), chlorpromazine (Thorazine), and phentolamine methanesulfonate (Regitine). It was the purpose of the present study to determine the effects of these compounds on aqueous flow by means of repeated tonography.

Methods

Male albino rabbits (Haskins Rabbitry, St. Louis) were used. Tonographic tracings were obtained with use of only topical anesthesia (tetracaine, 0.5%), as previously described.[1] By convention, tonography was carried out on the right eye first. In preliminary experiments it was found that the intraocular pressure and facility of outflow in most rabbits were approximately normal 60 to 90 minutes after the initial tonogram. Consequently, a recovery period of at least one hour, and usually two to three hours, was allowed before experimental treatment. The 1955 calibration data of Friedenwald [4] were used in the calculations of facility values.‡ The dosages and routes of administration of the compounds are given with the data in the Tables.

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† Becker, B., and Demorest, B.: Unpublished observations, 1954.

‡ Flow was calculated from the equation:

$$F=(P_o-9)\times C$$

where

F = flow (cu. mm/min.)
C = facility of outflow
P_o = intraocular pressure (mm.Hg).

Comment

Vasopressin.§—As discussed in more detail in another paper,[5] the finding of a decreased intraocular pressure after topical administration of vasopressin suggested the possible use of this compound in glaucoma therapy. Consequently, the effects of vasopressin were studied extensively in rabbits. The administration of 0.2 unit of vasopressin, subconjunctivally or topically, had little effect on intraocular pressure, outflow facility, or aqueous flow (Table 1). Careful sub-

TABLE 1.—*Effect of Vasopressin (0.2 Unit) on Aqueous Flow*

Rabbit No.	Treated Eye				Contralateral Eye			
	Before*		After†		Before		After*	
	P_o	C	P_o	C	P_o	C	P_o	C
326	25	0.24	22	0.22	24	0.24	21	0.21
304	22	0.19	17	0.17	21	0.18	18	0.20
305	27	0.15	22	0.16	27	0.15	24	0.14
459	20	0.16	20	0.27	17	0.15	20	0.16
327	21	0.37	16	0.24	20	0.40	17	0.30
403	22	0.20	24	0.27	21	0.21	19	0.19
404	17	0.22	17	0.26	16	0.26	21	0.18
436	20	0.27	17	0.20	21	0.27	21	0.23
325	24	0.24	23	0.20	22	0.22	15	0.16
Mean	22	0.24	20	0.22	21	0.23	20	0.20
No. of Eyes	9		9		9		9	
Change in flow			−21%				−20%	

*P_o, intraocular pressure (mm. Hg); C, facility of outflow.
† Values 45-60 minutes after subconjunctival or topical administration.

conjunctival injections of saline and chlorbutanol to controls were also found to have no effect.

Higher doses of vasopressin resulted in a decreased intraocular pressure in all eyes. Most rabbits showed a maximal fall of intraocular pressure in 45 to 60 minutes, lasting for 1½ to 2 hours. Repeated administration every 30 or 60 minutes failed to prolong the decreased aqueous flow after an effective dose of vasopressin (1 unit) or to increase the effectiveness of a relatively inactive dose (0.2 unit). The subconjunctival injection of a suspension of vasopressin in oil (Parke-Davis), although equally effective as the aqueous solution, also did not prolong the effect of drug. Intravenous administration of vasopressin produced symmetrical bipaterap decreases in intraocular pressure and aqueous flow of similar duration and effectiveness. However, the effects on pressure and flow after topical applications were usually more marked in the treated eye than the contralateral eye (Tables 2 and 3). Thus, at a dose of one unit, an average inhibition of flow of 62% was noted in treated eyes and there was only 30% decrease in the contralateral eye. The administration of 2 units resulted in 85% suppression of flow in the treated as compared with 61% in the opposite eye. In similar studies on human eyes, topical administration resulted in a suppression of aqueous flow, confined exclusively to the treated eye.[5] This may be due in part to a difference in dosage per body weight or to a more rapid systemic destruction or excretion of the antidiuretic hormone in humans. Considerably more variability of response was observed in rabbit eyes both as to time course and degree of effectiveness. No alterations in scleral rigidity were noted in either species.

§ An aqueous solution of Pitressin (Parke-Davis Company) was used.

TABLE 2.—*Effect of Vasopressin (1 Unit) on Aqueous Flow*

Rabbit No.	Treated Eye				Contralateral Eye			
	Before		After*		Before		After*	
	P_o	C	P_o	C	P_o	C	P_o	C
326	25	0.15	17	0.17	22	0.16	19	0.10
379	16	0.39	9	0.28	15	0.40	12	0.29
327	17	0.20	15	0.33	21	0.18	18	0.28
469	28	0.20	14	0.23	24	0.31	15	0.37
304	24	0.17	12	0.20	24	0.17	17	0.17
305	28	0.20	22	0.11	28	0.16	24	0.12
471	22	0.36	9	0.17	17	0.33	18	0.33
403	24	0.31	18	0.24	22	0.22	22	0.25
Mean	23	0.25	15	0.22	22	0.24	18	0.24
No. of eyes	8		8		8		8	
Change in flow			−62%				−30%	

* Values 45-60 minutes after subconjunctival or topical administration.

TABLE 3.—*Effect of Vasopressin (2 Units) on Aqueous Flow*

Rabbit No.	Treated Eye				Contralateral Eye			
	Before		After*		Before		After*	
	P_o	C	P_o	C	P_o	C	P_o	C
219	23	0.24	9	0.23	19	0.23	16	0.19
220	23	0.38	11	0.22	27	0.39	13	0.20
231	27	0.26	13	0.20	26	0.23	15	0.23
233	18	0.31	13	0.18	19	0.23	11	0.22
243	28	0.36	17	0.25	28	0.31	21	0.27
234	16	0.26	9	0.17	17	0.22	12	0.15
236	23	0.30	18	0.28	22	0.32	21	0.33
243	28	0.36	9	0.21	28	0.31	16	0.24
Mean	23	0.31	12	0.23	24	0.28	16	0.23
No. of eyes	8		8		8		8	
Change in flow			−85%				−61%	

* One hour after topical vasopressin.

It was of interest to observe that the majority of animals which sustained a decrease in aqueous flow of somewhat more than 60% presented a decrease in outflow facility (Table 3). Aldosterone [6] and fludrocortisone (9α-fluorohydrocortisone) [1] have been observed to potentiate the action of acetazoleamide in lowering intraocular pressure in rabbits. Tonographic tracings [1] suggested that the effects of these steroids were dependent upon the prevention of the compensatory decrease in outflow facility following acetazoleamide. However, the data in Table 4 indicate that fludrocortisone did not prevent the decreased outflow facility associated with the depression of flow following vasopressin. In fact, the results were almost identical with those found after treatment with 2 units of vasopressin alone (compare Tables 3 and 4).

Franceschetti and Schlaeppi [7] had observed previously the fall in intraocular pressure following vasopressin and the equal effectiveness of the systemic, subconjunctival, or topical administration. These investigators reported that the topical application of 0.05 unit to one eye caused a fall in intraocular pressure in the treated eye and a rise in pressure in the contralateral eye. In the present series, doses of 0.2 unit or less caused little change in pressure in either eye (Table 1).

The effect of vasopressin on iris vessels of six rabbits was observed with the aid of a Zeiss dissecting scope. The vessels constricted maximally, frequently with vasospasm, approximately 30 minutes after topical administration of 1 unit.

TABLE 4.—*Fludrocortisone and Vasopressin Effect on Aqueous Flow*

Rabbit No.	Treated Eye				Contralateral Eye			
	Before		After*		Before		After*	
	P_0	C	P_0	C	P_0	C	P_0	C
272	22	0.25	14	0.23	22	0.25	17	0.20
231	22	0.29	9	0.15	28	0.23	15	0.16
233	20	0.25	12	0.18	17	0.27	13	0.14
219	24	0.40	9	0.23	25	0.28	15	0.16
220	28	0.31	15	0.24	25	0.33	17	0.20
231	21	0.35	8	0.23	25	0.32	21	0.30
233	18	0.28	12	0.20	19	0.39	8	0.33
272	21	0.27	13	0.13	20	0.21	18	0.17
Mean	22	0.30	12	0.20	22	0.29	16	0.21
No. of eyes	8		8		8		8	
Change in flow			−85%				−61%	

* One hour after topical vasopressin and three hours after topical or subconjunctival fludrocortisone (0.15 mg.).

A more marked effect on the treated eye was usually apparent, but bilateral effects were sometimes noted. Recovery from the vasoconstrictive activity occurred generally in one and one-half to two hours and corresponded well with the recovery of aqueous flow and intraocular pressure. Repeated doses did not prolong the recovery period significantly. Similar refractoriness of animals to repeated doses of vasopressin has been noted by others.[8]

Thus, it may be concluded that vasopressin administration usually results in a decreased formation of aqueous humor, with a resultant decrease in intraocular pressure and a compensatory decrease in outflow facility. Further experimentation is required to elucidate the role of the local vasopasm as well as other mechanisms involved in the reduction of aqueous flow.

Chlorpromazine.—Chlorpromazine was given systemically, as it was ineffective by the topical route. The intramuscular injection of 0.3 to 0.5 mg/kg. body weight caused a decrease in intraocular pressure in all eyes. Intraocular pressure was decreased from an initial average of 18 mm. Hg to 13 mm. Hg by one and one-half hours, and this fall persisted for three hours. Aqueous flow was decreased an average of 72% at both time intervals (Table 5). The tendency for a decreased outflow facility to be evident when flow was suppressed more than 60% was observed after chlorpromazine much as after vasopressin or acetazoleamide. While these studies were in progress, Paul and Leopold[9] reported a fall in intraocular pressure in cats and rabbits following administration of chlorpromazine. It should be noted, however, that these workers used considerably larger doses of chlorpomazine (50 to 100 mg.) and recorded profound decreases in intraocular pressure persisting for six hours or more.

Phentolamine Methanesulfonate.—This drug was equally effective when applied topically or given systemically. At a dose of 0.1 to 0.2 mg. per animal (Table 6) a decrease in intraocular pressure was observed in both eyes from an average initial value of 21 mm. Hg down to 15 mm. Hg at 30 minutes and 14 mm. Hg at 2 hours. Aqueous flow was found to be decreased an average of 50% and 58% at these time intervals. Although there were individual exceptions, in general, the outflow facility of animals at these doses was not decreased. Increasing the dose to 0.3 mg. resulted in a further decrease in aqueous flow to 77% inhibition at one and one-half and three hours. Intraocular pressure was maintained at an

TABLE 5.—*Effect of Intramuscular Chlorpromazine (0.3-0.5 Mg/Kg.) on Aqueous Flow*

Rabbit No.	Before Treatment		After Treatment			
			60-90 Min.		180 Min.	
	P_o	C	P_o	C	P_o	C
220	18	0.26	10	0.22		
	17	0.36	15	0.35		
231	23	0.23	18	0.17		
	24	0.27	16	0.21		
233	13	0.30	12	0.18		
	14	0.28	10	0.18		
296	25	0.42			19	0.25
295	27	0.26			13	0.18
297	21	0.34			10	0.24
219	16	0.26	11	0.27	13	0.18
	17	0.12	9	0.13	13	0.18
174	25	0.18	16	0.10	15	0.08
	21	0.18	15	0.09	12	0.06
555	15	0.30	12	0.20	13	0.20
	15	0.26	9	0.17	10	0.13
556	20	0.33	18	0.21	19	0.26
557	16	0.29	13	0.20	14	0.24
560	18	0.23	14	0.23	15	0.24
	17	0.26	15	0.23	15	0.20
562	13	0.42	11	0.37	12	0.27
	13	0.39	12	0.20	12	0.24
566	17	0.27	11	0.24	10	0.13
565	17	0.25	16	0.15	15	0.25
568	19	0.10	15	0.07	13	0.07
	24	0.24	13	0.05	13	0.03
569	15	0.21	10	0.13	11	0.15
	19	0.35	10	0.11	12	0.11
489	20	0.18	..	.....	15	0.13
556	17	0.44	12	0.15	7	0.21
	13	0.31	10	0.20	12	0.23
Mean	18	0.30	13	0.19	13	0.18
No. of eyes	30		26		24	
Change in flow			−72%		−73%	

TABLE 6.—*Effect of Phentolamine Methanesulfonate (0.1-0.2 Mg.) on Aqueous Flow*

Rabbit No.	Before Treatment		After Treatment			
			30 Min.		120 Min.	
	P_o	C	P_o	C	P_o	C
466	27	0.35	16	0.38		
	25	0.21	17	0.27		
467	15	0.29	9	0.33		
	20	0.34	13	0.33		
468	24	0.35	21	0.30		
498	17	0.51			15	0.49
	15	0.44			11	0.42
502	21	0.54			15	0.43
	17	0.37			14	0.40
503	21	0.21			17	0.22
329	24	0.23	18	0.21	16	0.24
	21	0.26	12	0.20	15	0.28
331	22	0.22	22	0.25	20	0.21
	19	0.17	14	0.27	12	0.22
462	24	0.35	14	0.34	13	0.30
	27	0.32	15	0.26	23	0.19
463	21	0.34	12	0.32	10	0.29
	22	0.45	13	0.30	10	0.28
464	18	0.16	15	0.34	11	0.25
	21	0.16	17	0.17	16	0.19
465	17	0.33	12	0.37	12	0.35
	15	0.41	..	.....	13	0.39
Mean	21	0.30	15	0.30	14	0.30
No. of eyes	22		16		17	
Change in flow			−50%		−58%	

average value of 13 mm. Hg, however, because of a decrease in outflow facility. Outflow facility decreased on the average by some 30%, much as that observed after vasopressin or chlorpromazine.

TABLE 7.—*Effect of Phentolamine Methanesulfonate (0.3 Mg.) on Intraocular Pressure and Aqueous Flow*

Rabbit No.	Before Treatment		After Treatment			
			90 Min.		180 Min.	
	P_o	C	P_o	C	P_o	C
234	16	0.19	9	0.15		
	16	0.19	12	0.15		
236	22	0.25	15	0.39		
	21	0.27	19	0.32		
231	24	0.31			11	0.13
	28	0.31			15	0.14
233	15	0.24			9	0.12
	15	0.28			11	0.17
271	24	0.40			10	0.19
272	32	0.46			14	0.28
	30	0.42			22	0.22
384	21	0.33	11	0.19	10	0.27
	21	0.45	15	0.25	21	0.45
392	22	0.47	9	0.31	7	0.19
	22	0.40	13	0.23	12	0.23
385	17	0.30	15	0.19	15	0.18
	19	0.23	17	0.10	14	0.14
395	14	0.25	11	0.23	11	0.17
	15	0.23	12	0.18	15	0.24
Mean	20	0.32	13	0.22	13	0.21
No. of eyes	19		12		15	
Change in flow			−77%		−78%	

Comment.—Chlorpromazine is known to be an inhibitor of both divisions of the autonomic nervous system at the central nervous system level. It is thought to be more effective in blocking the sympathetic than the parasympathetic system, although the findings are not conclusive.[10] Linnér and Prijot[11] found that the removal of the superior cervical ganglion caused a profound fall in intraocular pressure lasting for 24 hours. This occurred without affecting episcleral venous pressure or outflow facility. Phentolamine methanesulfonate, a sympatholytic drug, may be the medical counterpart of sympathectomy in the rabbit. Rosen ‖ has observed that the ganglionic blocking agent pentolinium (Ansolysen) decreased aqueous flow and tended to cause a decrease in outflow facility. The findings of Linnér and Prijot suggest that the decreased intraocular pressure observed following the administration of all of these agents may be related to their sympatholytic action. In the present studies the decreased outflow facility was primarily manifested when aqueous flow was reduced somewhat more than than 60%. Further work is in progress to determine the mechanism of the decrease in facility of outflow observed following profound suppression of flow by any of these agents.

Summary

The effect of various doses of vasopressin, chlorpromazine, and phentolamine methanesulfonate on intraocular pressure and rate of flow of aqueous humor in rabbits has been studied by tonography. These compounds were found to lower intraocular pressure by means of a profound suppression of aqueous flow. The effective doses were 1 to 2 units of vasopressin, 0.3 to 0.5 mg. of chlorpromazine per kilogram of body weight, and 0.3 mg. of phentolamine methanesulfonate. Vasopressin and phentolamine methanesulfonate may be administered topically, but chlorpromazine was only effective when given systemically. In general, it was observed that when aqueous flow was suppressed somewhat more than 60%

‖ Rosen, D. A.: The Effects of a Ganglionic-Blocking Drug, Pentapyrrolidinium, on Ocular Fluid Dynamics: A Preliminary Report, read before the East Central Section of the Association for Research in Ophthalmology, Toronto, Jan. 9, 1955.

a compensatory decrease in outflow facility prevented further depression of intraocular pressure.

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Subepithelial Versus Subcapsular Injections of Drugs

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Subconjunctival injections of drugs commonly are used in ophthalmic therapeutics; however, little attention has been paid to the depth of injection. It apparently has been assumed that the subepithelial connective tissues of the bulbar conjunctiva are too thin to present an appreciable barrier to the passage of drugs. Recently, Schlegel and Swan have studied the ocular penetration of procaine by quantitative analysis of the tissues of the rabbit eye.[1] They found that the forward extension of Tenon's capsule represents a considerable barrier to the penetration of this anesthetic into the iris, aqueous, and cornea after injections just under the conjunctival epithelium. They designated this as a "subepithelial" injection. Furthermore, Schlegel

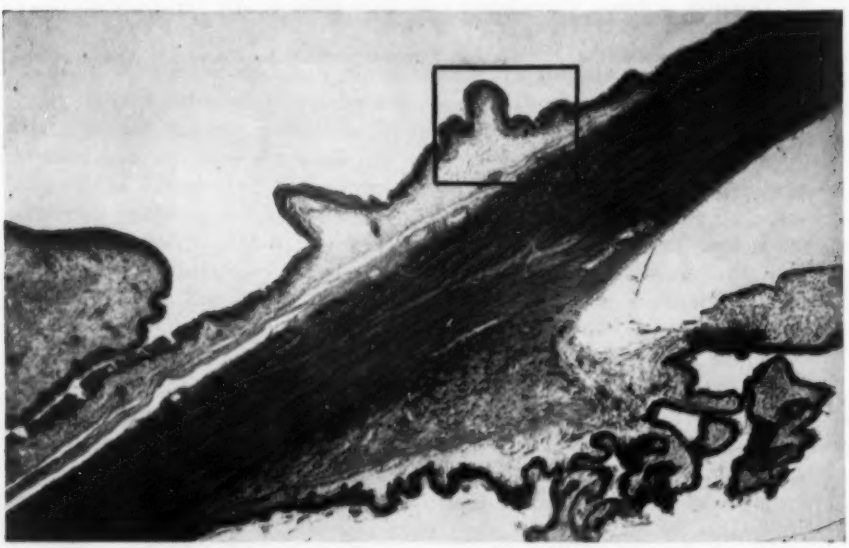

Fig. 1.—Low-power photomicrograph of the anterior segment, to demonstrate the normal relationship of the bulbar conjunctiva and forward extension of Tenon's capsule to the globe. The blocked area is the common site for injection of drugs.

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All illustrations in this paper are excerpts from a movie presented before the American Academy of Ophthalmology and Otolaryngology in Chicago, Oct. 13, 1955.

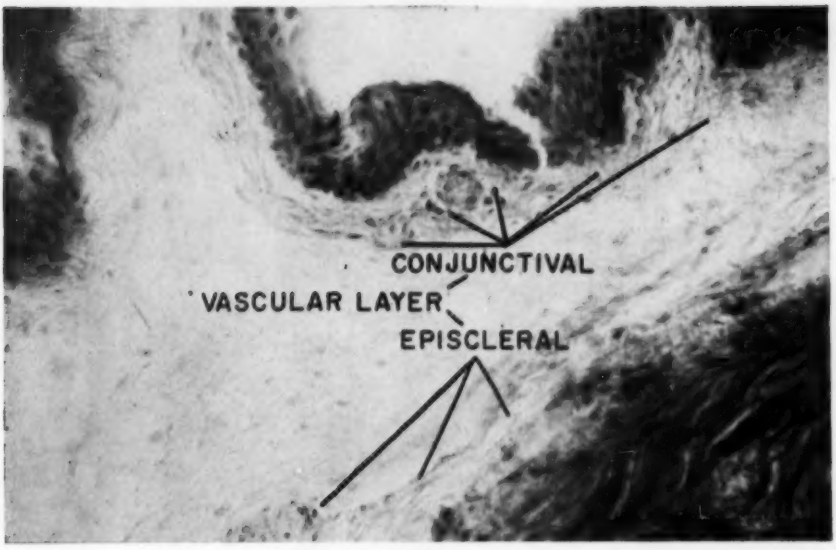

Fig. 2.—Enlargement of blocked area shown in Figure 1. The conjunctival vessels can be seen to lie just under the epithelium. The relatively avascular Tenon's capsule separates the subcapsular tissue level from the conjunctival circulation.

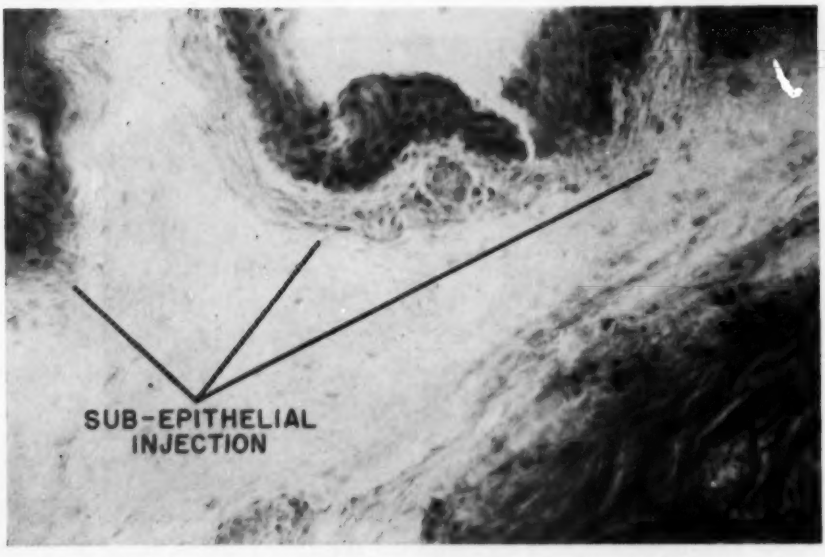

Fig. 3A.—Subepithelial injection. The drug is brought into close approximation with the conjunctival vessels and is rapidly carried into the general circulation.

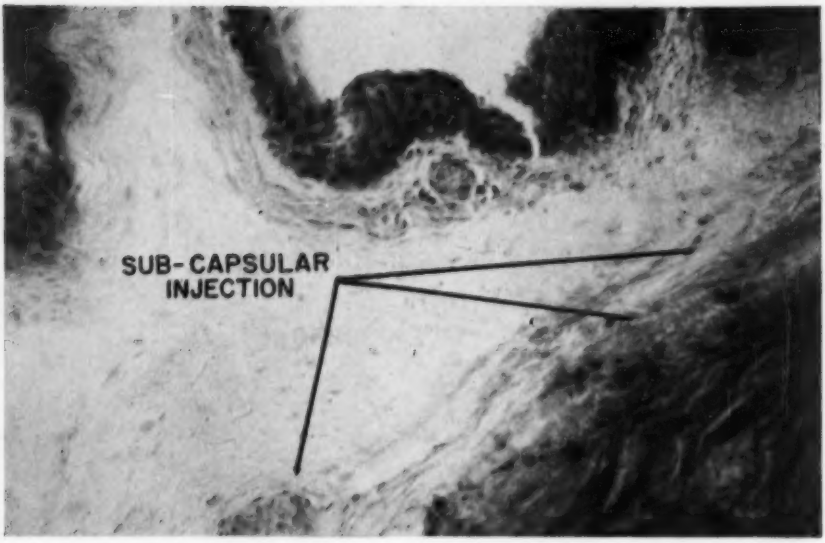

Fig. 3B.—Subcapsular injection. The drug is brought into direct contact with the episclera and limbic stroma.

and Swan found that after subepithelial injections the drug solution was carried away from this area via the conjunctival vessels. The addition of epinephrine for vasocontriction or cutting off the circulation significantly enhanced the penetration of procaine from the subepithelial tissues into the iris.

In contrast to subepithelial injections, those injections made beneath Tenon's capsule bring the drug solution into direct contact with the episclera

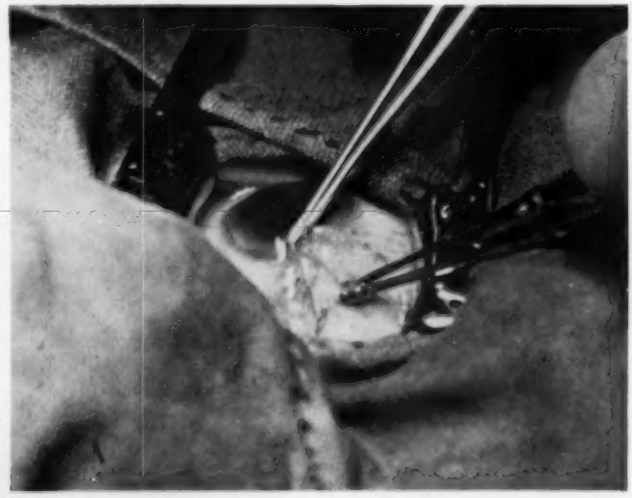

Fig. 4A.—Demonstration of the conjunctiva and Tenon's capsule during the course of a glaucoma operation in a middle-aged adult. The conjunctiva is folded down over the limbus. Tenon's capsule is being held in place.

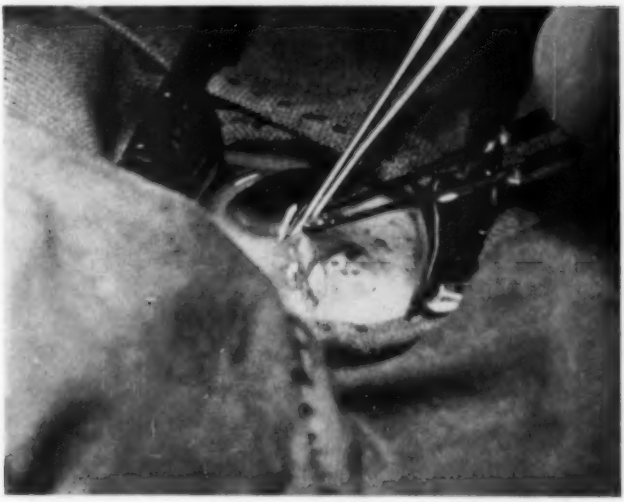

Fig. 4B.—Same situation as in Figure 4A. Tenon's capsule is also turned down to the limbus, baring the episcleral vessels.

and limbic stroma. These have been designated as "subcapsular" injections.[2] The subepithelial and subcapsular tissue levels, vascular layers, and sites of injection are illustrated in Figures 1 to 4. Judging by the concentrations of drugs in the iris, aqueous, and cornea of animal eyes, subcapsular injections are more effective than subepithelial injections.

We have been studying the comparative effectiveness of subepithelial and subcapsular injections in humans by observing and recording the time

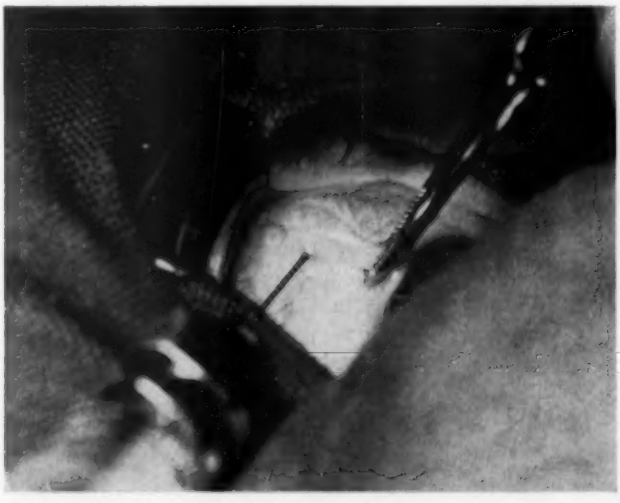

Fig. 5A.—Technique of anterior subcapsular injection. Both conjunctiva and Tenon's capsule are elevated with forceps. The needle is passed under Tenon's capsule several millimeters behind the limbus. The tip of the needle then can be brought forward so the injection is made close to the limbus.

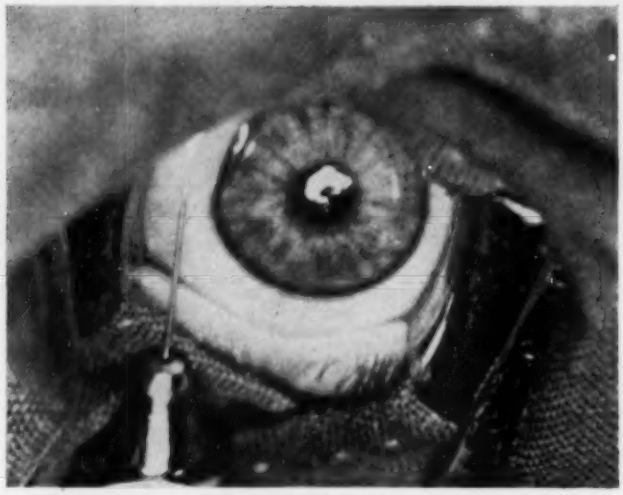

Fig. 5B.—Technique of sub-epithelial injection. The needle is between the conjunctival epithelium and Tenon's capsule.

of onset and degree of pupillary changes induced by the injection of autonomic drugs. In this respect epinephrine, in spite of its vasoconstrictor effects, has been particularly useful in that it induces a segmental contraction of the iris dilator near the site of injection. The techniques of injection are illustrated in Figures 5A and 5B.

The pupillary changes that occur when 0.05 cc. of a 1:1000 concentration of aqueous solution of epinephrine hydrochloride is injected under the epithelium on one side of the eye and under the anterior capsule on the other side of the same eye were studied in 12 patients who received a general anesthetic (ether) for strabismus surgery. Three of these patients were adults; nine were children between the ages of 7 and 14. The pupils were made miotic by instillations of 0.5% pilocarpine nitrate two hours before surgery. In 11 of the 12 patients the pupil dilated more rapidly on the side of the subcapsular injection. Generally, the onset of the dilatation of the pupil on the side of the subcapsular injection began 5 to 6 minutes after the injection of the drug solution, whereas onset of the dilatation on the side of the subepithelial injection generally did not begin until 10 to 16 minutes. In the following illustrations (Figs. 6 to 9), pupillary changes were recorded at 4, 8, 12, and 16 minutes after the injections were made in the eye of a 7-year-old child. We have concluded from these clinical studies, and also from the quantitative tissue analyses, that there generally is a significant difference in the rate of penetration of drugs into the anterior segment from the subepithelial compared with the subcapsular tissue level. In most younger patients, subcapsular injections will be considerably more effective. It is considered that in some patients with atrophy or unusual thinness of the subepithelial connective tissue that there might be less difference, but this remains to be established by additional study.

Fig. 6.—Pupillary size four minutes after 0.05 cl. of 1:1000 epinephrine hydrochloride has been injected 2 to 3 mm. from the limbus into subepithelial tissue (left) and at the subcapsular level (right). The patient is a 7-year-old child under ether anesthesia. Pilocarpine nitrate, 0.5%, has been instilled one hour previously to induce miosis.

Fig. 7.—Eight minutes after the injection, mydriasis has begun on the side of the subcapsular injection (right).

Fig. 8.—Twelve minutes after the injection. Continued contraction of the iris dilator on the side of subcapsular injection (right).

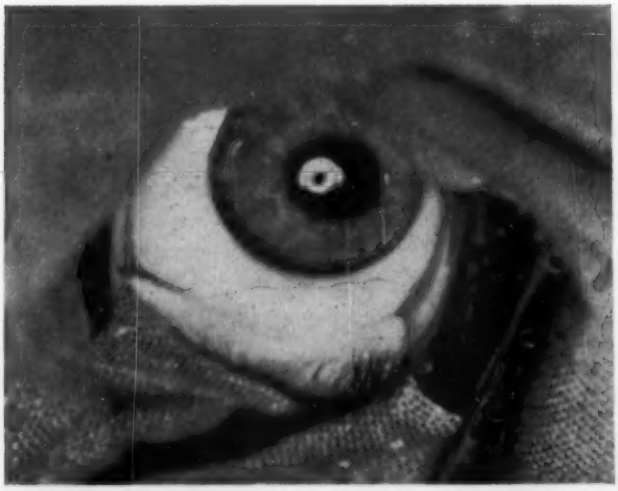

Fig. 9.—Sixteen minutes after injection. Mydriasis is just beginning on the side (left) of the subepithelial injection, in contrast to nearly completed maximal dilatation on the side (right) of the subcapsular injection.

Summary

Subconjunctival injections can be made just under the epithelium but external to Tenon's capsule (subepithelial) or beneath Tenon's capsule in direct contact with the episclera and limbic stroma (subcapsular). Judging from the time of onset and degree of segmented contraction of the iris dilator induced by epinephrine, subcapsular injections generally are a more effective means to administer drugs to the anterior segment than subepithelial injections.

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An Experimental Evaluation of Scleral Shortening Operations

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The penetrating scleral resection operation, as advocated by Lindner [1] in 1933, salvaged many previously hopeless cases of retinal detachment. Following this advance in detachment therapy, the full-thickness scleral resection became accepted by most opthalmic surgeons. However, the frequent operative complications of hemorrhage and vitreous loss during full-thickness sclerectomies prompted the development of safer scleral shortening operations.

The lamellar-scleral resection, as advocated by Dellaporta,[2] Paufique,[3] and Shapland,[4] has gained increasing usage in recent years. Schepens * further modified the lamellar-scleral resection by infolding polyethylene tubing in the base of a lamellar-scleral preparation. Recently, I reported a new type of scleral shortening operation,[5] the scleral fold, which seems to offer certain advantages.

These modified scleral shortening procedures represent the basic improvements in operative technique since Müller first devised the scleral resection, 53 years ago, for use in myopia. In all these years there has been little experimental consideration of this subject. Borley [7] studied the alteration in the measurements of the globe following scleral resections in enucleated dog eyes. Scheie [8] measured the immediate and prolonged volumetric changes in dog eyes following shortening by penetrating scleral resections and scleral shrinkage from surface diathermy. Dellaporta [2] compared the penetrating scleral resection and the lamellar-scleral resection in dog eyes. His paper offers the only microscopic study of the response of the globe to scleral resection.

The following study was conducted in an effort to evaluate and compare all the basic scleral shortening operations in use, with emphasis on the microscopic findings.

Experimental Procedure

The four basic scleral shortening operations considered in this study follow:

1. Penetrating (full-thickness) scleral resection
2. Lamellar-scleral (partial-thickness) scleral resection
3. Lamellar-scleral resection with infolded polyethylene tubing
4. Scleral fold (outfolding)

A. General Operative Procedure.—Chinchilla rabbits weighing an average of 2.5 kg. were

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From the Department of Ophthamology of Columbia University College of Physicians and Surgeons, and the Institute of Ophthamology of the Presbyterian Hospital.

*Schepens, C.: Symposium: Retinal Detachment, New York Academy of Medicine, Section of Ophthalmology, Jan. 3, 1955.

used. Each operation was performed in an equatorial direction about 7 mm. from the limbus. The length of each resection was 8 to 10 mm., being limited by the distance between the emissary vessels, which are more numerous in rabbits than in man. Lowering the intraocular pressure was necessary to lessen the tension on the sclera and allow scleral shortening in these animals. This was accomplished by paracentesis of the anterior chamber with removal of about 1.5 ml. of aqueous, thus making the globe soft enough to reduce the scleral area. Operations were performed on the left eye of 64 rabbits, the right eye serving as a control. These 64 animals included 16 examples of each of the four types of operations.

B. Procedure for the Four Basic Operations.—1. Penetrating Scleral Resection: A full-thickness strip of sclera averaging 8 mm. long and 1.5 mm. wide was excised with Stevens scissors. The scleral wound was closed with five single-armed 00000 mild chromic absorbable surgical (gut) sutures.

2. Lamellar-Scleral Resection: Dissections averaging 8 mm. in length and 1.5 mm. in width were made with a Bard-Parker knife. The dissection was attempted to a depth equivalent to the lamina fusca in man. The wound was closed with four mattress sutures of 00000 mild chromic absorbable surgical sutures.

3. Lamellar-Scleral Resection with Polyethylene Tubing: This procedure was performed in a manner identical with the lamellar-scleral operation, except that polyethylene tubing was shaped to fit and was applied to the resected scleral area. The lamella of sclera with the polyethylene tube was infolded with four or five mattress 0000 black nonabsorbable surgical silk sutures in half of this group and with 00000 mild chromic absorbable surgical suture in the remaining half. A tendency toward extrusion of the polyethylene tubing, noted early in the experiment, necessitated a change from absorbable (gut) suture to silk suture in this group.

4. Scleral Fold Operations: Folds of sclera averaging 8 to 10 mm. in length and including 2 mm. of sclera in the fold were maintained by four or five mattress 00000 mild chromic absorbable surgical sutures. The sclera and choroid were separated with a cyclodialysis spatula preceding the creation of the fold.

All the animals operated on were rated and equally distributed into survival groups of 4, 10, 21, and 45 days. Four examples of each of the four types of operation, 16 animals, made up each of the four survival groups. Fundus and gross anatomic studies were recorded at the completion of the operation and at the time of killing. Serial celloidin sections were prepared for microscopic study.

Results

A. Fundus Observations

In the immediate postoperative period the retina was detached to compensate for the reduced ocular volume in all cases. The amount of detachment did not vary significantly with the type of shortening procedure. Detachment was in the form of several irregular ridges of retina with intervening furrows. In the lamellar-scleral and polyethylene tubing operations the main ridge of detachment tended to be more regularly in line with the direction of the scleral incision. The retinal ridges were flattened and the retina reattached in most instances by the 21st postoperative day. Frequently, fine pigment striae of the retina marked the areas previously detached.

Choroidal, retinal, or vitreous hemorrhage could usually be accounted for in the operative protocol. Bleeding from the emissary vessels and vitreous loss often resulted in vitreous hemorrhages and subsequent vitreous band formation. These complications were consistently more frequent in the penetrating scleral resections. The scleral fold procedures were accompanied by more frequent choroidal hemorrhage than the lamellar-scleral and polyethylene tubing operations. Separation of the sclera and choroid with the spatula seemed responsible for this change. These hemorrhages of the choroid were readily absorbed, with little remaining evidence, by the 21st postoperative day.

B. Gross Observations

At the completion of the operation all globes were flattened in the area of operation. By the fourth postoperative day the globes had regained their spherical shape. The anterior chambers were consistently re-formed in one day.

In the penetrating resections and lamellar-scleral preparations it was difficult to determine the exact status of the scleral wound, because scar tissue obscured differentiating features. In the scleral folds the ridge of sclera was readily identified and evaluated. The fold was present in all 21-day preparations, with a tendency of the central sutures to pull free. At 45 days there were small areas of scleral transparency and the scleral fold had flattened. The polyethylene tubing was found on the surface of the sclera, encapsulated by scar tissue, in all the 21-and 45-day specimens, even when silk sutures were employed. This effect was seen earlier and more consistently with the use of absorbable (gut) suture.

C. Results of Microscopic Study

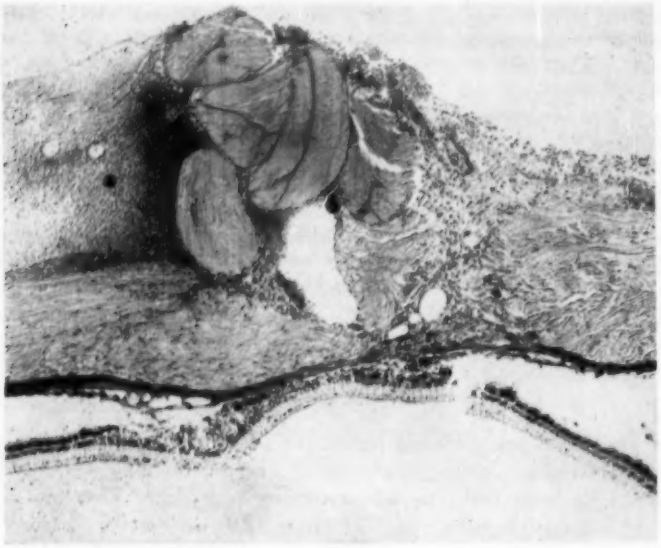

Fig. 1.—Scleral resection (four days postoperative).

1. *Four-Day Preparation.*—(*a*) Penetrating Scleral Resection (Fig. 1): The wound is well approximated and shows healing by the elements of both episclera and suprachoroid. A subsiding acute inflammatory reaction about the sutures and wound is noted. A moderate to severe chorioretinitis is seen in all of the penetrating scleral resection operations at this time. In other procedures where no chorioretinitis is present, an artifactual detachment of the retina during fixation occurs. This can be differentiated from a true detachment of the retina, which is accompanied by a subretinal transudate.

(*b*) Lamellar-Scleral Resection (Fig. 2): There is a moderate invagination of the lamella of sclera in all the four globes of this group. The healing, which can take place only from the episcleral portion of the wound, is characterized by a relatively mild fibroblastic response. The wound surface shows a subsiding

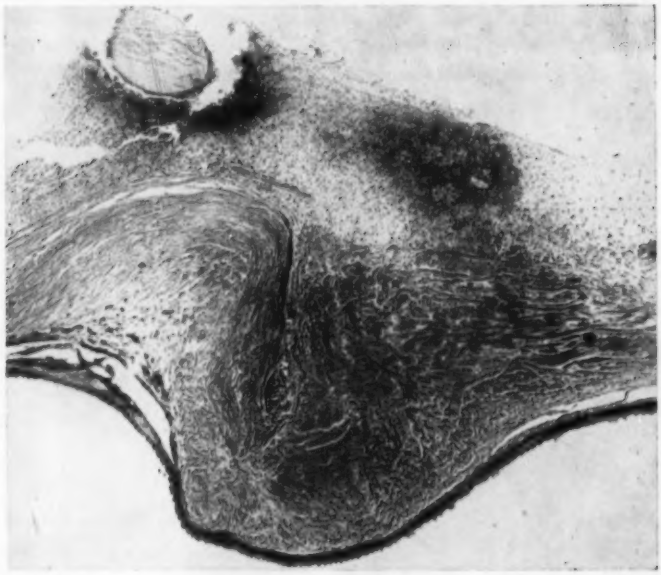

Fig. 2.—Lamellar-scleral resection (four days postoperative).

acute inflammatory reaction. A "dead space" on either side of the infolded scleral lamella is filled by a swollen choroid with some transudation, in all sections. None of the sections show signs of chorioretinitis.

(*c*) Lamellar-Scleral Resection with Polyethylene Tubing (Fig. 3): All sections show the tubing well covered by a thick layer of sclera. The episclera shows a mild fibroblastic response to wound healing. A rounded invagination of the

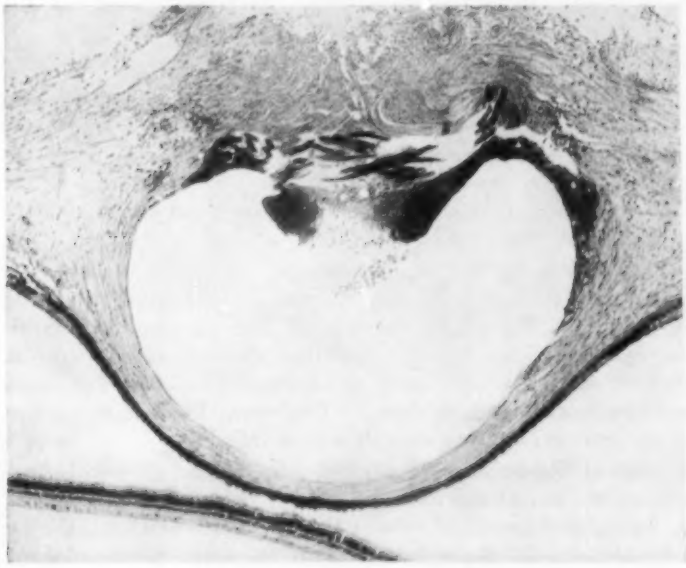

Fig. 3.—Lamellar-scleral resection with polyethylene tubing (four days postoperative).

scleral lamella conforms to the shape of the embedded tubing, which was dislodged during sectioning. An adjacent "dead space," similar to that seen in the lamellar-scleral resection, is noted in all four eyes. There is no chorioretinitis.

(*d*) Scleral Fold (Fig. 4): The sclera is maintained in a well-defined fold

Fig. 4.—Scleral fold (four days postoperative).

by the gut suture, in all sections. Some fibroblastic response of the episclera can be seen invading the scleral fold along the tract of the suture; however, the predominant response to the wound healing can be seen to arise from the suprachoroid. The choroid is intact, but is congested, and shows a moderate chorioretinitis in most of the sections. The retina is thrown into a compensatory fold, due to the scleral-shortening effect.

2. *Ten-Day Preparation.*—(*a*) Scleral Resection (Fig. 5): Fairly good apposition of the scleral wound edges is seen in three of the preparations, while the fourth globe showed some gaping of the wound. The suprachoroidal contribution to wound healing appears more marked than that of the episclera. A chronic inflammatory reaction is seen about the sutures. The choroid is intact but shows a moderate chorioretinitis in three of four eyes. There is destruction of the outer cellular elements in those eyes showing a retinitis.

(*b*) Lamellar-Scleral Resection (Fig. 6): A considerable chronic inflammatory reaction about the wound and sutures is noted. There has been a marked recession of the invaginated lamella of sclera. Wound closure is maintained by a mild fibroblastic response of the episclera. That there is little reaction of

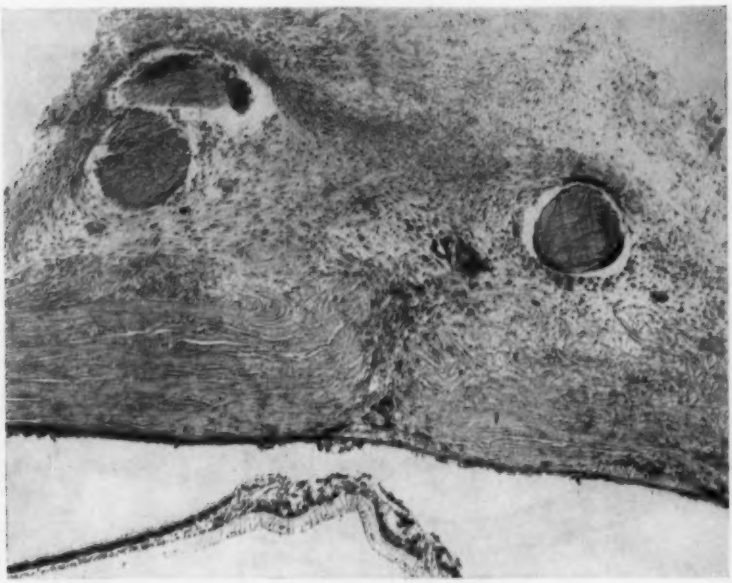

Fig. 5.—Penetrating scleral resection (10 days postoperative).

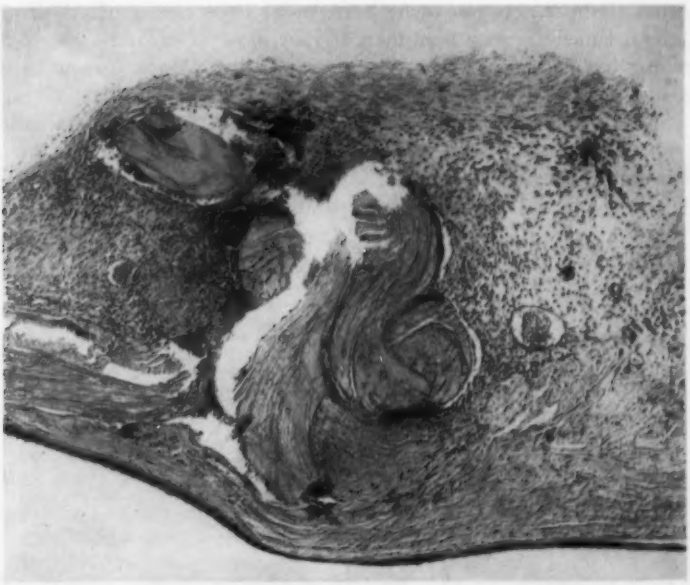

Fig. 6.—Lamella-scleral resection (10 days postoperative).

the choroid or retina is evidenced by an artifactual separation of the retina in the wound area.

(*c*) Lamellar-Scleral Resection with Polyethylene Tubing (Fig. 7): There are considerably fewer scleral fibers overlying the tubing by this time. A moderate

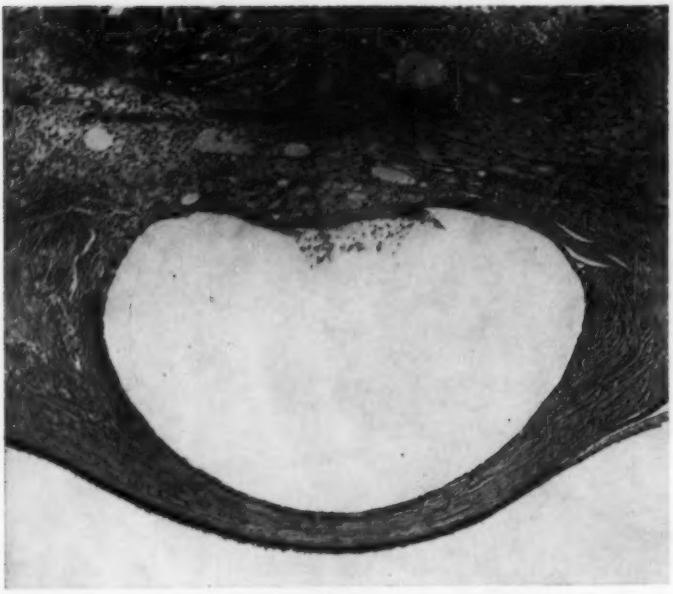

Fig. 7. — Lamellar-scleral resection with polyethylene tubing (10 days postoperative).

replacement of sclera by fibrous tissue is seen over the tubing in all sections. This fibrous tissue has begun to infiltrate around the tubing. Less invagination of the scleral lamella is seen here than at four days. The "dead space" adjacent to the tubing has flattened out, and little choroidal reaction is present in the four specimens.

(*d*) Scleral Fold (Fig. 8): A moderate chronic inflammatory reaction is present about the fold. The fold is intact in all instances, and the line of coaptation of the sclera is usually not visible. The base of the fold had flattened. Atrophic changes in the folded sclera are seen. There is a moderate chorioretinitis

Fig. 8.—Scleral fold (10 days postoperative).

in half of the preparations. Two samples show little or no chorioretinal adhesions. In the Figure shown, a mild chorioretinitis with a serous retinal detachment is seen.

3. *Twenty-One-Day Preparation.*—(*a*) Scleral Resection (Fig. 9): A chronic

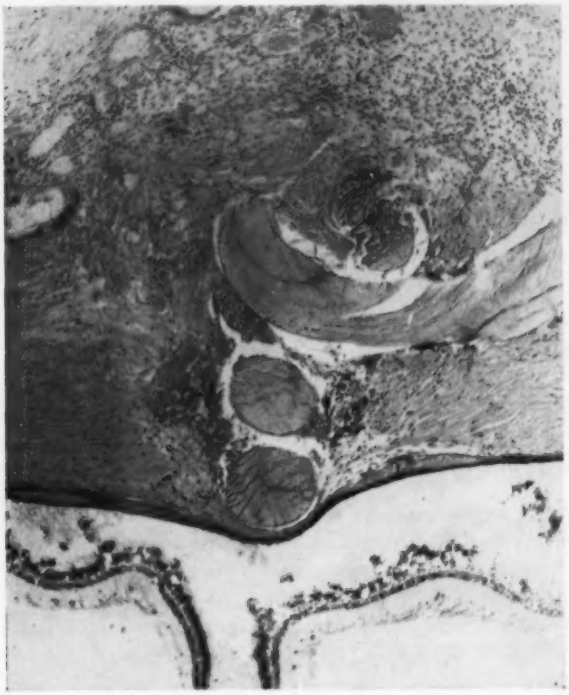

Fig 9.—Scleral resection (21 days postoperative).

Fig. 10.—Lamellar-scleral resection (21 days postoperative).

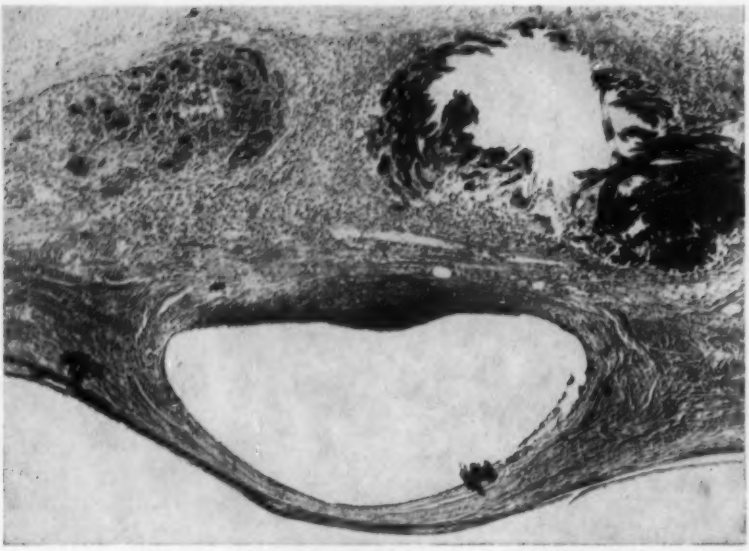

Fig. 11.—Lamellar-scleral resection with polyethylene tubing (21 days postoperative).

inflammatory reaction about a well-maintained wound is present in most cases. There is still some engorgement of the choroid. Folds of the retina, with some disruption of the retinal elements, can be seen.

(*b*) Lamellar-Scleral Resection (Fig. 10): The inflammatory response is subsiding and is characterized by giant cells. Little invagination of the scleral lamella remains in any of the preparations. There appears to be a tendency toward stretching of the wound edges.

(*c*) Lamellar-Scleral Resection with Polyethylene Tubing (Fig. 11): A

Fig. 12.—Scleral fold (21 days postoperative).

chronic inflammatory reaction with giant cells is seen in the wound area. Only a few scleral fibers overlie the tubing in all sections. Further outward displacement of the tubing is noted. There is a loss of nuclei of the fibers of the scleral lamella. The choroid is normal.

(*d*) Scleral Fold (Fig. 12): Giant cells surround the sutures and the fold of sclera. The scleral fold is maintained throughout more than half of the area of operation in all sections. There is a definite loss of nuclei of the scleral fibers, particularly in the folded zone. The area pictured shows no evidence of chorioretinitis. This finding is true of two of the four eyes studied.

4. *Forty-Five-Day Preparation.*—(*a*) Penetrating Scleral Resection (Fig. 13): Some irregularity and thinning of the scleral fibers adjacent to the chronic

Fig. 13.—Penetrating scleral resection (45 days postoperative).

inflammatory episcleral reaction mark the operative site. This was noted in all sections. A healed chorioretinitis with definite destruction of retinal elements is seen in about half of the sections.

(*b*) Lamellar-Scleral Resection (Fig. 14): There is a consistent suggestion of unfolding of the operative wound in all the preparations of this group. A marked chronic inflammatory reaction filling the operative base is seen. None of the sections showed signs of chorioretinitis.

(*c*) Lamellar-Scleral Resection with Polyethylene Tubing (Fig. 15): A thick fibrous capsule is seen surrounding the tubing in all sections. Few, if any, scleral fibers are present over the surface of the tubing. In sections where the sharper edges of the polyethylene were placed against the scleral lamella there is a strong tendency for the tube edges to cut through the sclera. The choroid and retina are normal in all cases.

(*d*) Scleral Fold (Fig. 16): A distinct fold cannot be seen in any of the sections. Infiltration of the wound site by fibrocytes is extensive. In most sections the sutures have, in effect, excised the fold of sclera. Some thinning of the retina at the site of previous chorioretinitis is seen in about half the sections.

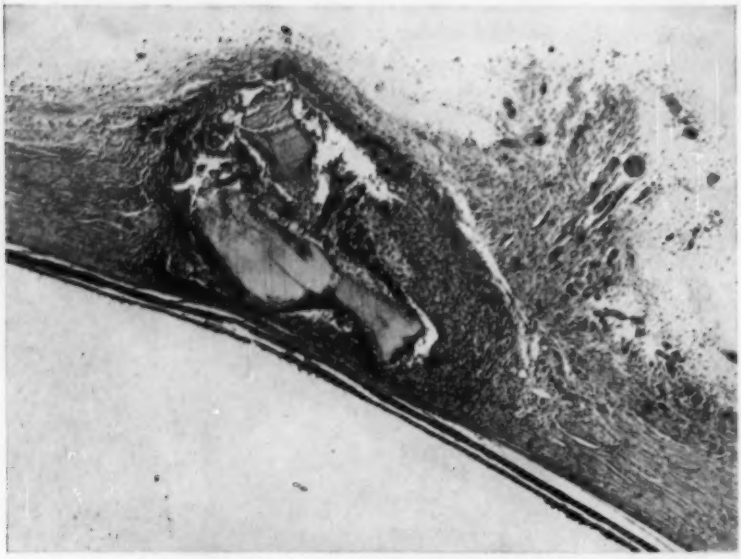

Fig. 14.—Lamellar-scleral resection (45 days postoperative).

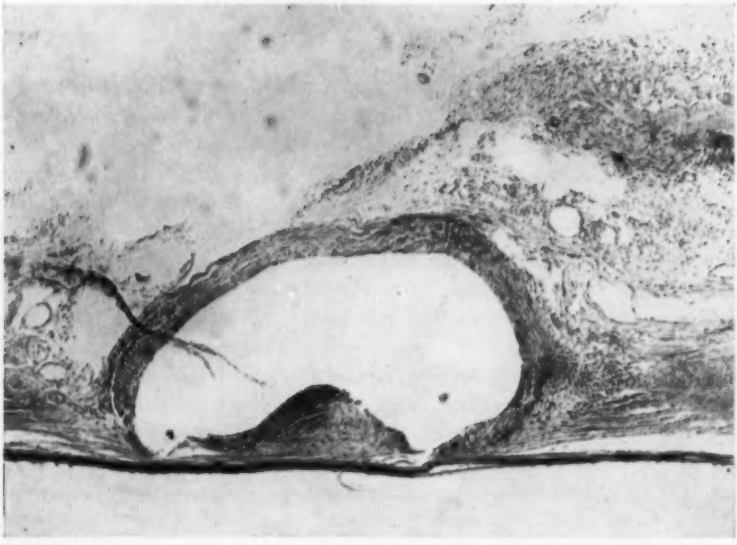

Fig. 15.—Lamellar-scleral resection with polyethylene tubing (45 days postoperative).

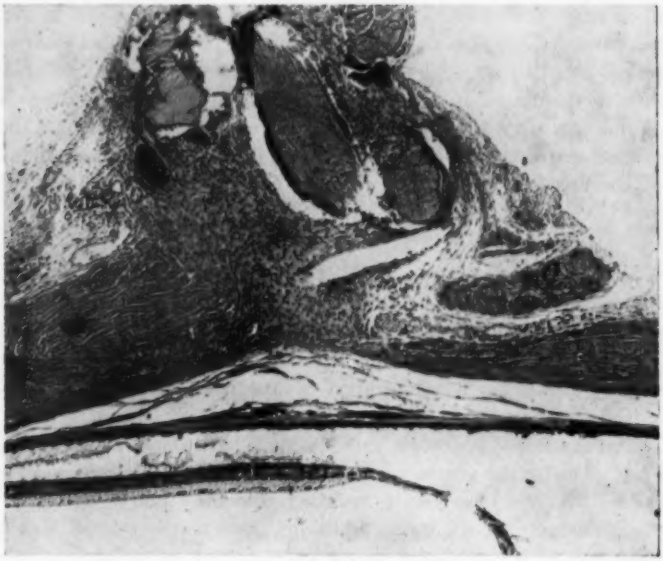

Fig. 16.—Scleral fold (45 days postoperative).

Comment

It is more difficult to perform scleral shortening operations in the smaller rabbit eye than in human eyes, but this is equally true of the different types of operations studied. An evaluation of the results of these comparative experimental operations can be applied to clinical practice.

The nature of the vitreous body is the most important difference between this experimental situation and conditions encountered in a scleral shortening operation in humans. Owing to the well-formed, healthy rabbit vitreous, scleral shortening can only be achieved by reduction of the ocular volume by paracentesis of the anterior chamber. Frequently the ocular pressure is elevated following experimental scleral shortening in spite of this paracentesis. In this study the anterior chamber invariably re-formed within the first postoperative day. The postoperative tension on the wound as a result of reduced scleral area, a healthy vitreous, and a re-forming anterior chamber must be considered in evaluating wound healing. This may account for some of the loss of nuclei of the scleral fibers seen in most of the preparations. This pressure effect is relatively equal in the different operations, being proportionate to the reduction of scleral area, and it creates a severer test of each shortening operation.

The vitreous body in clinical retinal detachment is usually abnormal and is associated with subretinal fluid, which is released at operation. Seepage of subretinal fluid postoperatively is permitted by drainage points in the sclera. The amount of pressure on the operative wound in humans is not as prolonged or as great as that occurring under experimental conditions, so the shortening effect is probably more permanent. However, despite the apparent temporary nature of experimental shortening, an interpretation of the ease and effectiveness of the scleral operations in rabbits seems applicable to clinical practice.

Certain aspects of this study suggested modification of the scleral fold oper-

ation as originally described. The easy creation of the scleral fold at the extremes of the unspatulated portion of the operative site, without inclusion of choroid in the folded sclera, suggested abandonment of any separation of choroid from sclera with a spatula. Also, the advantages of promoting healing from both episcleral and suprachoroidal tissues suggested excision of the top of those scleral folds in which more permanent shortening is desired.† Excision of the fold has confirmed the freedom of the choroid from the scleral fold when spatulization is not utilized.

Conclusions

Certain advantages and disadvantages are associated with each operation studied. The penetrating scleral resection heals readily with minimal wound reaction, because both episcleral and choroidal cellular responses are permitted. However, this advantage is outweighed by the inordinate frequency of serious operative complications.

The lamellar-scleral operation and the lamellar-scleral operation with polyethylene tubing cause the greatest inward displacement of choroid, with infrequent complications, which is desirable in most detachments. The invagination of sclera in these experiments is of short duration, particularly in the lamellar-scleral preparatons, and to a less extent in the polyethylene procedures even when silk suture is used. Healing of the scleral wound in these two operations arises exclusively from the episclera and is a less active process than the response of the suprachoroid.

The scleral fold operation is accompanied by more frequent choroidal hemorrhage when preoperative spatulization is used. Scleral shortening, which is comparatively well maintained, is obtained by this procedure. In an unexcised scleral fold healing is mainly from the suprachoroid; however, excision of the fold, as suggested by this study, should allow episcleral tissue to contribute to healing.

The ideal scleral shortening operation should give maximum reduction of scleral area of a permanent nature, with the least incidence of operative complications. The penetrating scleral resection gave the best wound healing in this study but was accompanied by excessive complications. The lamellar-scleral type of procedure gave the least complications but less permanent shortening. This study suggested modifications of the scleral fold operation which should satisfy the criteria for efficient and safe shortening.

Summary

A brief review of the current status and previous experimental studies of scleral shortening operations in retinal detachment is presented.

A comparative study in rabbits of the four basic shortening operations in use today was conducted and is described. The procedures compared were the penetrating scleral resection, the lamellar-scleral resection, the lamellar-scleral resection with polyethylene tubing, and the scleral fold. The gross, opthalmoscopic, and microscopic results of this comparative experiment are presented.

The manner in which the scleral wound heals and is maintained was determined by long-term microscopic study. The results of these studies revealed advantages and disadvantages of each type of operation. The desirable features of each procedure suggest a modified scleral fold operation, which should most

†Experimental studies of these modifications will be reported at a later date.

nearly fulfill the criteria for safe and effective scleral shortening in retinal detachment surgery.

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Ocular Chrysiasis

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Chrysiasis, a deposition of metallic gold in human tissues, may occur after repeated parenteral administration of gold salts. Reported cases of gold impregnation of the ocular tissues are sufficiently rare to warrant inclusion of the present case in the literature.

The ocular changes which may be observed after intensive gold salt therapy for arthritis, tuberculosis, and lupus erythematosus have been adequately summarized by Thomas.[1] It is apparent that metallic gold may be deposited in the corneal stroma, in Descemet's and Bowman's membranes, and in the conjunctiva.* Some investigators have implied that the reduction of gold salts and the eventual deposition of gold particles in the tissues occurs mainly in those areas which have been exposed to light; however, perusal of the literature suggests that gold deposition may occur anywhere within the reticuloendothelial system and the connective tissue.†

Report of a Case

A 44-year-old white housewife was referred to the ophthalmology clinic at the University of Michigan Hospital on Dec. 28, 1955, from the Rackham Arthritis Research Unit for routine ocular examination. There were no symptoms referrable to the eyes. The past history revealed that she had been affected with chronic rheumatoid arthritis since 1935 and had been followed by the arthritis unit as a research patient since 1939. During the period from October, 1939, through May, 1948, the patient had received eight courses of intramuscular gold therapy representing a total dosage of 4555 mg. of gold sodium thiomalate N. F. (Myochrysine), 1235 mg. of sodium succinamide aureate, and 2185 mg. of aurothioglucose in oil (Solganol-B Oleosum).

Ocular examination was entirely normal except for the biomicroscopic examination of the conjunctiva, cornea, and lens. This disclosed throughout the entire conjunctiva numerous minute irregular brownish depositions located at various depths within the tissue. These were not apparently related to the blood vessels. When the beam of the slit lamp was passed over these particles, they were seen to have a golden metallic gleam. The cornea contained a much larger number of similar particles, which were especially numerous and practically contiguous in the region of Descemet's zone. They also appeared to be scattered rather uniformly throughout the stroma of the entire cornea but became less numerous as one approached the region just beneath Bowman's zone. A few particles were adherent to the anterior lens capsule. There was no evidence of inflammation in any of the tissues. The biomicroscopic appearance was essentially the same for both eyes.

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Department of Ophthalmology (Dr. Roberts) and Laboratory of Neuropathology and Neuro-Ophthalmology, Neuropsychiatric Institute (Dr. Wolter), University Hospital.

* References 2-7.

† References 9 and 10.

Fig. 1.—Cornea of the patient as seen with the slit lamp (drawing reconstruction).

On Jan. 2, 1956, small excisions were taken from the bulbar conjunctiva of the left upper fornix and from the skin of the upper lid in the region of the lid fold. The tissues were immediately fixed in formalin, embedded in paraffin, and cut in serial sections on the microtome. The majority of the sections were then stained faintly with hematoxylin, while the remainder were prepared according to the technique of Borchardt-Michaelis [11] for the histologic detection of gold.

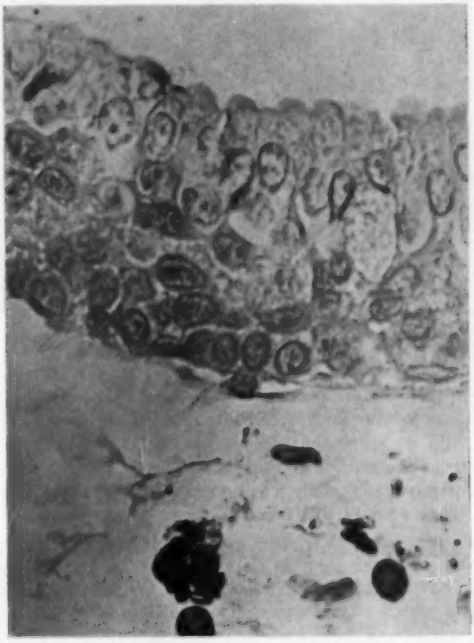

Fig. 2.—Single granules and large conglomerations of gold in the subepithelial connective tissue of the conjunctiva. Photomicrograph; × 800.

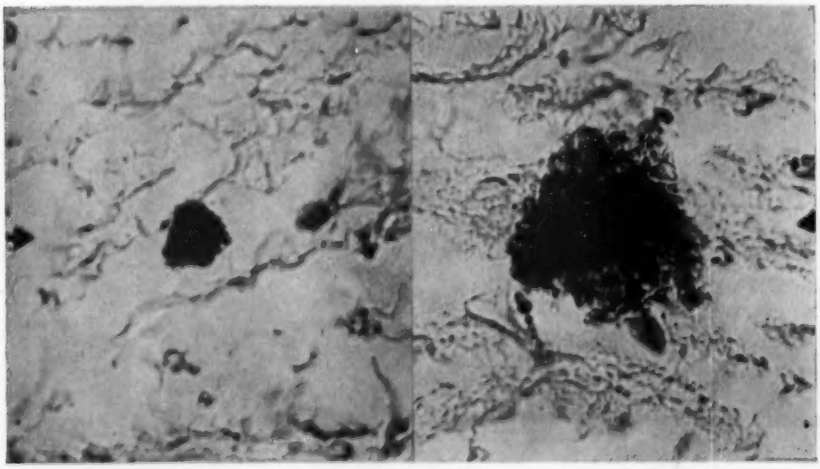

Fig. 3.—Two conglomerations of gold granules in the connective tissue of the conjunctiva (arrows). Photomicrograph; × 800.

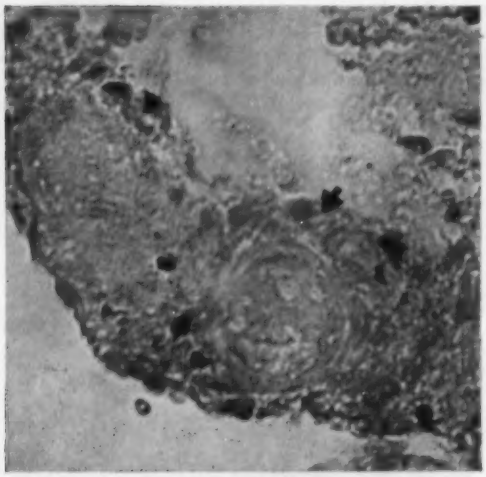

Fig. 4.—Two small blood vessels of the conjunctiva (arrows) with gold granules in the perivascular tissue. Photomicrograph; × 800.

The faint staining with hematoxylin of the sections of both conjunctiva and skin made it possible to recognize with the microscope the presence of numerous irregularly arranged black deposits of different sizes. The method of Borchart-Michaelis demonstrated that all of these deposits in both tissues were metallic gold. These crystal-like granules varied in size from 0.05μ to 0.2μ in diameter. They occured singly and as large conglomerations.

The gold particles were observed in both the subepithelial and epithelial layers of the conjunctiva. In the subepithelial layer the particles were found free in the connective tissue, within fixed connective tissue cells, within wandering histiocytes, and in the perivascular tissue. Histiocytes filled with gold granules were observed in the deeper layers of the epithelium. Free gold in conglomerate masses was seen among the epithelial cells and on the surface of the conjunctiva. In none of the sections was there foreign-body reaction or cellular evidence of irritation or inflammation.

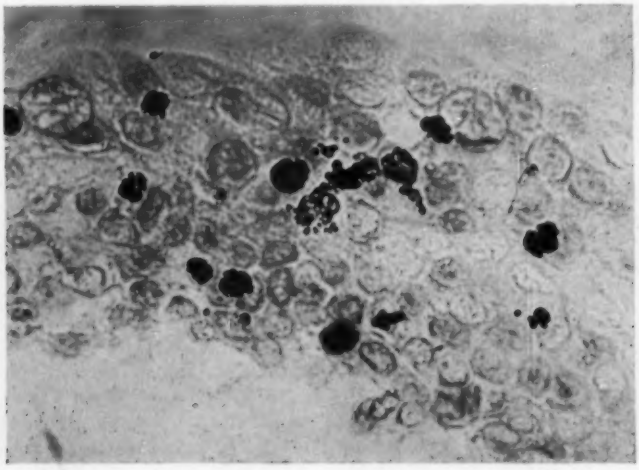

Fig. 5.—Conglomerations of gold in all layers of the conjunctival epithelium. In the basal layer there is a histiocyte filled with gold granules (arrow). Photomicrograph × 800.

The position of the gold in the dermis of the skin of the lid was essentially the same as that in the subepithelial layer of the conjunctiva. In contrast to the conjunctiva, no gold was seen in the epithelium of the skin, although there were many particles in the connective tissue just below the epidermis. Again, there was no evidence of foreign-body reaction.

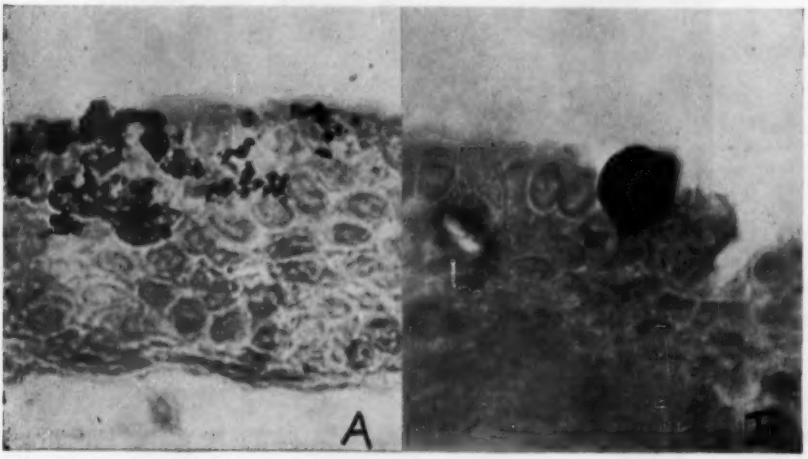

Fig. 6.—*A*, gold granules among the epithelial cells in the superficial layers of the conjunctival epithelium. *B*, large conglomeration of gold at the surface of the conjunctival epithelium. Photomicrograph; × 800.

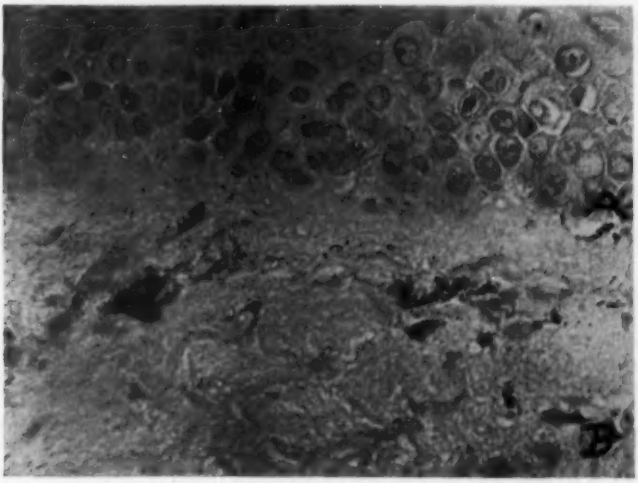

Fig. 7.—Gold granules in the dermis (*B*). The epithelium of the skin of the lid (*A*) contains no gold granules. Photomicrograph; × 350.

Comment

The clinical detection of biomicroscopic deposits in the conjunctiva and cornea and on the anterior lens capsule of a patient who had been subjected to intensive gold therapy for arthritis led to several interesting observations. Histologic study of a conjunctival biopsy disclosed these particles to be gold.

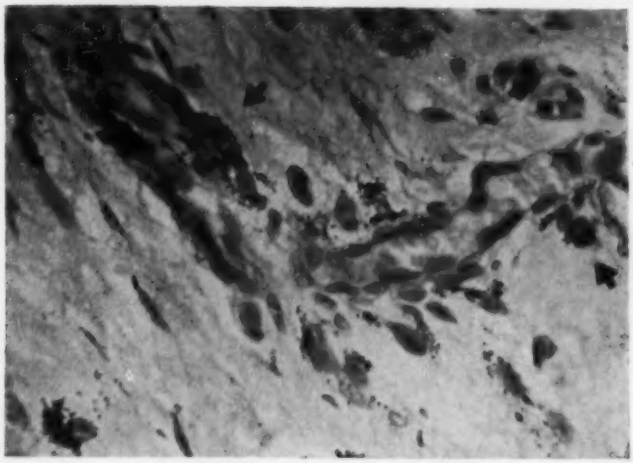

Fig. 8.—Small blood vessel of the skin of the lid. The perivascular tissue contains gold granules (arrows). Photomicrograph; × 800.

Furthermore, it appears that the conjunctiva seems to finally extrude the foreign material from the body. While it was not possible to study histologically tissue from the cornea or lens, the clinical similarity between the granules in the various tissues suggests that they are all the same material.

Another point of interest, not entirely answered in this paper, is the relationship of light as an adjunct to the deposition of gold within the tissue. Since the conjunctival biopsy specimen was obtained from the upper fornix, it would seem that light is not a specific requisite of this phenomenon.

Summary

The clinical and pathological description of a case of ocular chrysiasis is presented.

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The Effect of Cortisone on Experimental Pseudomonas Corneal Ulcers

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and
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The therapeutic use of cortisone in ocular inflammations has been increasing rapidly during the past few years. Adverse effects as in herpetic dendritic ulcers [1] as well as beneficial effects as in nongranulomatous uveitis [2] have been reported. The purpose of this paper is to report experimental evidence that cortisone may adversely modify Pseudomonas corneal infections in rabbits.

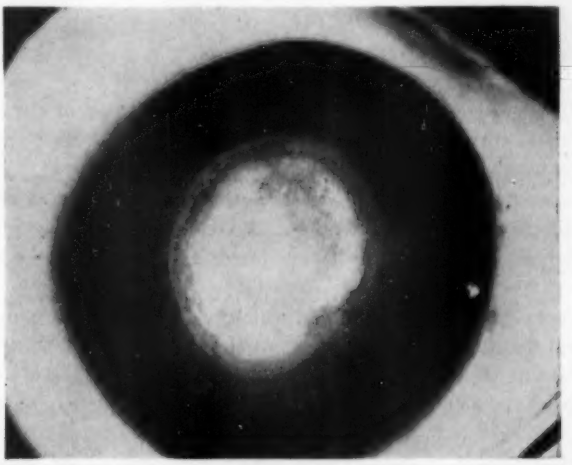

Fig. 1.—A typical Pseudomonas central corneal ulcer produced in a rabbit receiving cortisone.

Methods and Materials

Animals.—Both pigmented and albino rabbits of varying weights were used throughout. None of these animals had a history of past infections.

Bacterial Culture.—Pseudomonas aeruginosa organisms which were recently isolated from a human corneal ulcer were used throughout this study. The organisms were grown on tryptose agar slants at 37 C for 24 hours. Two drops (about 0.12 cc.) of an isotonic saline suspension containing 1,000,000,000 organisms per milliliter were used as the inoculum for each eye. Tetracaine (Pontocaine) hydrochloride U. S. P. (0.5%) was used topically in all the eyes.

Procedure.—The animals were divided into four groups and treated as follows:

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Melvin S. Rheins, Ph. D., performed the serologic studies.

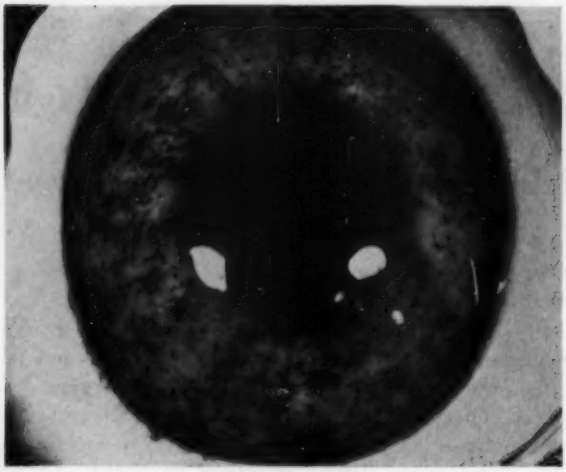

Fig. 2.—A typical minimal superficial corneal involvement in a rabbit receiving Pseudomonas without cortisone therapy.

Group I consisted of 14 rabbits which received 2 drops of the suspension of organisms on the cornea of each eye. Immediately both corneas were subjected to scarification with a hypodermic needle.

Group II comprised 11 rabbits which were given cortisone (Cortone) acetate (1 mg/per injection) subconjunctivally 24 hours before, immediately before, and 24 hours after the inoculum was placed on the corneas and the corneas were scarified.

Controls consisted of four animals which were treated the same as those in Group I except that the corneas were not scarified, four animals which were treated as those in Group II but the corneas were not scarified, and two rabbits which did not receive Pseudomonas or cortisone but were subjected to corneal scarification.

Group III consisted of four rabbits which were treated the same as Group I except that polymyxin B (1 mg/per injection) was inoculated subconjunctivally 24 hours before scarification, at the time of scarification, and 48 hours after scarification.

Group IV consisted of four rabbits which were treated as those in Group I with the exception that both polymyxin B (1 mg/per injection) and cortisone were given subconjunctivally 24 hours before and at the time of scarification and contact with the organisms.

Serology.—Four animals from each of Groups I and II were bled by intracardiac puncture 5 days and 11 days after the treatment described above. Aqueous humor was also obtained from these animals at the 11-day interval. Agglutination tests were performed on all these samples.

Cultures were taken from the eyes of selected experimental rabbits at various intervals after the infections. In all cases pure cultures of P. aeruginosa were isolated in thioglycollate broth (without indicator).

Results

As may be seen in Table 3, 54% of the rabbit corneas in Group II (cortisone-treated) demonstrated two-thirds to entire depth invoivement of the cornea, while

TABLE 1.—*Results Obtained the Tenth Post-Inoculation Day*

Rabbit No.	Cortisone	Corneal Scarification	Pseudomonas Inoculation	Results* O.D.	Results* O.S.
414	X	X	X	Full depth	Full depth
436	X	X	X	Full depth	Full depth
408	X	X	X	Negative	Full depth
429	X	X	X	Negative	Negative
430	X	X	X	Superficial	One-third
431	X	X	X	One-third	One-half
412	X	X	X	Superficial	Full depth
409	X	X	X	Full depth	Full depth
886	X	X	X	One-third	Full depth
171	X	X	X	One-half	Full depth
178	X	X	X	One-half	Full depth
167	X	X	X	Two-thirds	One-third
405	X	X	X	Full depth	Superficial
406	X	X	X	Full depth	Full depth
416		X	X	Superficial	Superficial
417		X	X	Superficial	Superficial
437		X	X	Superficial	One-third
438		X	X	Negative	Negative
442		X	X	Superficial	Superficial
443		X	X	Full-depth	Full-depth
410		X	X	Superficial	Superficial
147		X	X	Superficial	Superficial
117		X	X	One-third	Superficial
166		X	X	One-third	Superficial
435		X	X	One-thurd	One-third
No. of corneas (Controls)					
8	X		X	Negative	Negative
8			X	Negative	Negative
4		X		Negative	Negative

* Results indicated in terms of the depth of anterior corneal involvement. Superficial involvement generally occurred only in areas of scarification.

TABLE 2.—*Results Obtained the Tenth Post-Inoculation Day*

Corneas, No.	Cortisone	Polymyxin B	Corneal Scarification	Pseudomonas Inoculation	Results O.D.	Results O.S.
8	X	X	X	X	Negative	Negative
8		X	X	X	Negative	Negative

TABLE 3.—*Summary of the Results in Table 1*

Category	Full Depth No.	Full Depth %	Two-Thirds Depth No.	Two-Thirds Depth %	One-Half Depth No.	One-Half Depth %	One-Third Depth No.	One-Third Depth %	Superficial No.	Superficial %	Negative No.	Negative %
Non-cortisone-treated...	2/22*	9	0/22	0	0/22	0	5/22	23	13/22	59	2/22	9
Cortisone-treated.....	14/28	50	1/28	4	3/28	11	4/28	14	3/28	11	3/28	11
Polymyxin B-treated...	0/8	0	0/8	0	0/8	0	0/8	0	0/8	0	8/8	100
Polymyxin B-and-cortisone-treated.....	0/8	0	0/8	0	0/8	0	0/8	0	0/8	0	8/8	100

* Number of eyes involved in this category/total number of eyes in this group.

only 9% of those in Group I (non-cortisone-treated) demonstrated the same corneal manifestations. On the other hand, only 22% of the corneas in Group II demonstrated superficial or no involvement of the corneas, as compared with 68% in Group I. Animals treated with polymyxin B or polymyxin B combined with cortisone showed no corneal involvement.

The work presented here also indicated that abrasion of the cornea is a prerequisite for the development of Pseudomonas ulcers, since animals which were not scarified did not show corneal infection.

Grossly visible corneal ulcers in Group I were detected within 24 hours after

scarification, as contrasted to Group II (with the exception of one animal), which demonstrated no apparent corneal involvement during this period. However, 48 hours after scarification animals in Group II revealed corneal ulcerations which, in the majority of cases, exceeded those in Group I both in size and depth.

No agglutinins against Pseudomonas could be demonstrated either in the sera or in the aqueous humor in Groups I and II. This would indicate that the marked differences of corneal involvement between these two groups were not a function of antibody depression by cortisone. An alternate possibility would be based on a modification of the cellular defense mechanisms of the ocular structure by this hormone, since it has been shown that cortisone does have a blocking effect on inflammatory reactions and thus would encourage the spread of the infection.

Comment

Corneal ulcers due to P. aeruginosa have always been a constant source of apprehension to the ophthalmologist. Fortunately, however, we have at our disposal polymyxin B—an antibiotic which has been shown to be highly specific for many strains of Pseudomonas.[3] Because of the increased use of cortisone and cortisone-antibiotic combinations in ocular inflammations, this study was instigated to determine the effect of cortisone on experimentally produced Pseudomonas corneal ulcers in rabbits.

The results obtained would indicate that cortisone may modify adversely the course of the infections, since the majority of rabbits receiving this steroid developed a severer corneal lesion than those not receiving cortisone. On the other hand, steroids given concurrently with polymyxin B did not seem to effect the beneficial action of the antibiotic. From this, it would appear that if cortisone is prescribed the effective antibiotic must also be prescribed. Obviously, cortisone incorporated with a noneffective antibiotic would be no better therapeutically than the steroid alone. Thus the possibility would exist that the clinical course of the infectious corneal ulcer might be more devastating. It must be remembered, however, that different strains of Pseudomonas may vary in invasiveness.

These findings are in complete agreement with the statement by Thygeson and his co-workers[4] that "great care should be exercised in the use of cortisone and hydrocortisone in central corneal ulcers and that bacteriologic diagnosis should be made prior to employment of these hormones."

Summary and Conclusions

Pseudomonas corneal ulcers in rabbits were treated with cortisone, polymyxin B, and a combination of the two drugs.

Cortisone without a specific antibiotic may adversely modify the course of Pseudomonas corneal infections in rabbits.

The clinical significance of these findings is discussed.

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Notes on the Life and Work of George Bartisch

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A few observations on the activities of George Bartisch, that sixteenth century surgeon and ophthalmologist, might not only stimulate interest in a great personality but emphasize a few of the actualities of medical practice in his time. The sixteenth century saw speculation yielding to exact observation, with a multiplicity of facts rapidly replacing fiction and superstition.* It was then that the daring discoveries of Vesalius and Harvey, the pioneer work of Paré, the tremendous labors of Leonardo da Vinci and Paracelsus were blazing a trail through the darkness into the light of modern science. Bartisch's appearance on the German scene gave an encouraging impetus to the advancement of ophthalmic surgery. The title of "father of modern ophthalmology" bestowed upon him by medical historians appears well deserved.

Conforming to the prevailing practice, surgeons traveled extensively, offering their arts and exhibiting their skills. Most of them, however, never attained any particular prominence, and after their death they were soon forgotten, but not so George Bartisch. Without formal schooling, but, as Shastid [2] so aptly describes him, "simply a genius" with that invaluable faculty for the perception and interpretation of the obscure, he attained notable success, advancing the frontiers of medicine in general and ophthalmology in particular.

Of his early life little is known. Indeed, nothing would have been known about him had he not put into print his experiences and his attainments embracing part of his life. Although he was unable to attend higher schools of learning, still it becomes obvious from his writings that he had acquired more than a general minimum education. In the preface to his "Augendienst" there appears this statement: "Because of my inability, due to financial circumstances, to attain higher education and reach the faculty, I had to confine myself to surgery. For this I have always had an inclination and love."

His list of twelve requisites for those entering the field of eye surgery gives a fair conception of Bartisch's ethics. "An oculist and surgeon should: (1) Be descended from religious parents (2) Be religious himself (3) Have studied Latin, anatomy, the science of medicine (4) Be a surgeon, have learned the barber-trade from youth on; not suitable are those that come to it from the plow, manure-wagon, etc., and late in life (5) Have studied with an accomplished oculist and surgeon (6) Have healthy and young eyes (7) Have fine, subtle, healthy hands and fingers, and be nimble with both

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* Reference 1, p. 38.

hands. Those who are not adept with the left hand and have to work on the cataract from the back are apt to produce a blind patient (8) Must be able to draw (design) in order to obtain instruments (9) Must be married (10) Must not be greedy for money or be haughty (11) Not a drunkard (12) Not audacious (presumptuous) or vainglorious." Then, as an afterthought, "Very few such oculists exist."

His travels took him through Saxony and Silesia, but in the latter part of the 16th century he settled in Dresden, where he was appointed court oculist to the Elector of Saxony. Some pertinent records are to be found in the Dresden archives.[3] In 1585, twice in 1588, and again in 1597 he was issued a renewal by August of Saxony of an open letter of recommendation enumerating items relative to expenses and safe conduct, this being sort of a traveling passport, which was not to be openly displayed but to be shown to the town-counsellor of each place visited. In July of 1583, he received from Kaiser Rudolph copyrights covering his books and again from the elector August the same Saxon privilege for all his future writings. On June 22, 1588, the Counsellor of the City of Znaim (in Moravia, Czechoslovakia) solicited the counsellors of Dresden to give Bartisch permission to operate on George Schultz, the blind vicar of the Church of St. Michael. The widowed queen of Denmark (1593) in a letter from Wolfenbüttel (Brunswick, Germany) asks if Bartisch would be able to travel anywhere when called. In 1583, a news item in the City Chronicle of Gõrlitz (in the Prussian province of Silesia) imparts the information that Bartisch operated for cataract on the twin brothers Dressner with a beneficial result. All of this "aura popularis" apparently followed the appearance of his "Augendienst" in 1583. As so frequently happens in medical practice, fame and fortune will often befall an author subsequent to the publication of an illustrious work.

Judging from the list of more than 85 testimonials in the forepart of his book, Bartisch must have developed a substantial practice, with a good following and a rather fair amount of success, since he was able to muster so many notarized depositions and affidavits, all authenticated by authoritative persons. Inasmuch as the testimonials present cures only, it can be assumed that his practice far exceeded the number of patients documentarily presented in his case histories. Undoubtedly, dissatisfied patients, who were submitted to unsuccessful surgery, were not approached and so were not included in the list. No actual figures concerning the results of eye surgery of that period are available. However, it can be reported of at least one contemporary surgeon that of fifty cataract operations, only four patients obtained some vision.[4] Applying this ratio to Bartisch, it is conceivable that he enjoyed a large eye-practice.

German physicians were by necessity itinerant. They went gypsy not because of "wanderlust," but rather for financial reasons. The distribution of handbills became a necessity in the various towns listed in their itinerary, but with competition rising additional measures had to be employed to attract the crowds and the recalcitrant patient. These procedures were not limited to quacks, but were utilized by well-recognized physicians and surgeons. Accordingly, the Chronicle of the city of Memmingen reports: "On the second of July there arrived a famous physician, by name of Johann

Christian Huber, with five carriages, among them two very magnificent ones. He was accompanied by fifty attendants, including women and children, a female dwarf, two Hungarian man-servants, two trumpeters, and several good musicians, who were accomplished on the French horn. There were eighteen horses and two camels. He set up his stage on the square called the Rat's Moat, sold his wares, gave performances before and after, and was surrounded by well-dressed and well-mannered persons."

However, only a few could indulge in this ostentatious form of advertising. Consequently handbills became a more popular way of soliciting patients, used alike by charlatans and legitimately famous physicians, who were true masters in their specialities, including Bartisch. A few of his handbills, in a fairly good state of preservation in the Library of Dresden, reveal colorful sidelights. None of them are limited to eye conditions exclusively. It is found that one of them urges those suffering pains and aches of the teeth and gums to seek the help of George Bartisch. Another of these "throw-aways" discourses on the subject of cystic calculi, at the same time mentioning "cataract, catarrh, bad inflammation or other ailments of the eyes, those whose hearing is reduced or obstructed; who have in their heads or ears sensations of roaring, whirring, hissing, ringing and singing, with defective hearing." It further counsels and advises those with the following afflictions to present themselves to George Bartisch, and a blank space follows for the insertion of the name of the inn for Bartisch's temporary residence in town: "people who have on their bodies large unnatural growths, goiters, exostoses, varicose veins. . . congenital cleft palate or harelip . . . people who have on their bodies large long-existing diseased patches, such as cancer, fistula, lupus." According to present standards, Bartisch would hardly be called an ophthalmologist, but owing to his singular achievements in diseases and surgery of the eye, there is general agreement that he helped sow the seeds of modern ophthalmic science.[6]

The year 1600 finds Bartisch in Vienna, but the success of this visit can hardly have contributed to his most pleasant memories.[7] In November, 1579, he applied in Vienna for admission to medical examinations but was rejected by the medical faculty. This rejection occurred probably on the strength of a decision of the faculty that examinations should be restricted to such persons in the medical field who could bring proof that they were either citizens of Vienna, or that the City of Vienna had promised them rights of citizenship. Itinerants participated everywhere in the medical examinations in order to use the certificates for purposes of advertising. The regulations of the faculty were intended to protect the public against incompetents, as well as to eliminate competition for the resident surgeons.

Every year, around Nov. 25, a big fair was held in Vienna, the so-called St. Catherine's Fair. On this occasion there assembled from far and near such wayfaring personages as gypsies, jugglers, theriamerchants, herbalists, surgeons, and others. During this period, peripatetic medical practitioners were permitted to practice, provided they had previously submitted their certificates to the Dean. George Bartisch visited the Fair in 1600 and did such a thriving business that he asked for permission to stay on a few more days. However, the regulations were very strict, and Bartisch was asked to leave by the end of the current month.

A true itinerant, Bartisch was not frightened by such actions of the controlling medical bodies, with whose practices he had long since become familiar. He returned, but only for a short time, because on Jan. 10, 1601, the Guild of Barber Surgeons accused him before the medical faculty, which in turn asked energetically that the authorities intervene; this they did, and Bartisch was forced to depart. This trip was probably one of his last, for he had then reached the age of 66. He died six years later, in 1607.

Bartisch wrote two books, one in 1575 on "cutting for stone" and the other in 1583 under the Greek title "Οφθαλμοδουλεια [Ophthalmodouleia] das ist Augendienst." The former was never considered of great value and did not make the grade; the latter, a masterpiece, became the first independent compilation of an ophthalmological treatise written in the German language,[6] inaugurating a definite advance in the management of diseases of the eye. The first edition of this work is a large folio volume, usually bound in vellum, but also occurring in blind-stamped pigskin or calf over wooden boards. Some copies exist with clasps and catches attached. The book consists of 548 pages of text, with 28 preliminary and 8 appended leaves. The title is in red and black within a fine woodcut border. Following this is a large woodcut portrait of Bartisch, as well as full-page arms of the Duke of Saxony and of Dresden. The illustrations are remarkable, including 88 large and interesting woodcuts. The colophon at the bottom of the last page reads as follows: "Printed in Dresden by Matthes Stockel, 1583,"

Fig. 1.—Colophon of first edition of "Augendienst."

with a quotation from Psalms 33:22, "Let thy mercy, O Lord, be upon us, according as we hope in thee" (Fig. 1). Some of the anatomical illustrations were copied after Vesalius, but most of them, including those of surgical procedures and instruments, were made after drawings by Bartisch himself.

A smaller second edition appeared in 1584, differing from the first only in some differences of the title page and bearing the name of a different printer (printed in Frankfurt, A.M. Sigsmundi Feyerabends). Undoubtedly, it continued to be a practical ophthalmic handbook, because after 103 years, in 1686, it was reprinted in Nürnberg by the publishing firm of George Scheurer under the title of "Georg Bartisch' Augendienst." The format of this last work is small quarto, in contrast to the first edition, which appeared in large folio. This last edition contains fewer illustrations than the two earlier ones; the sixteenth chapter, dealing with the preparation of different medications, has been deleted, but the volume is enriched with an alphabetically arranged subject index. It would be expected that the illustrations showing surgical procedures at least display one hundred years of anatomical and surgical progress, but only the costumes have been modernized to conform with the times; otherwise the procedures remain unchanged.

To those cherishing a love for more detailed information about the

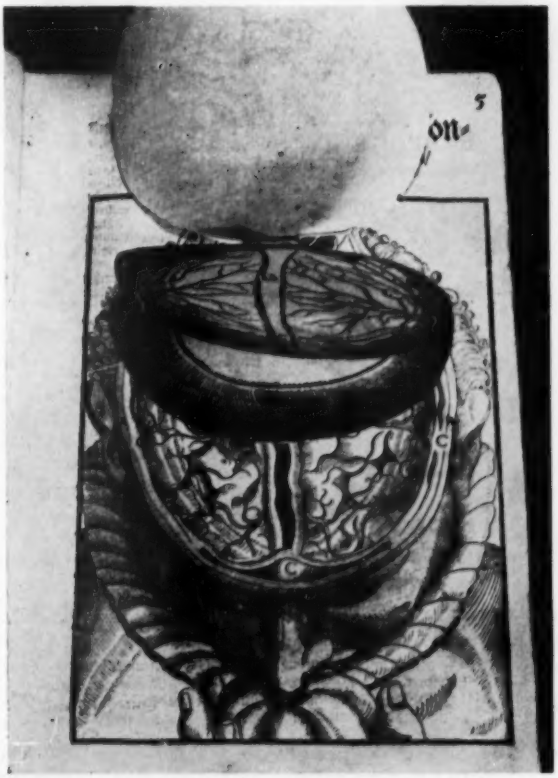

Fig. 2.—Plate showing the corresponding positions of superficial and deeper parts, with superimposed sections.

text, a brief résumé of each chapter should be gratifying. To the modern physician and surgeon, this should be of more than passing interest, not only demonstrating the early crudities of a half-forgotten age, but revealing the problems of a specialized medical field in its incipient stage.

Chapter one, describing the anatomy of the head and eye, includes two noteworthy figures, each consisting of several superimposed sections, which reveal the corresponding positions of the superficial and deeper parts (Fig. 2).

In the second chapter, Bartisch considers congenital defects, including imbalances of the extraocular muscles. For children with this affliction he constructed head-hoods, with correspondingly arranged holes, similar to the antecedent Greek masks and of course quite as useless (Fig. 3). For

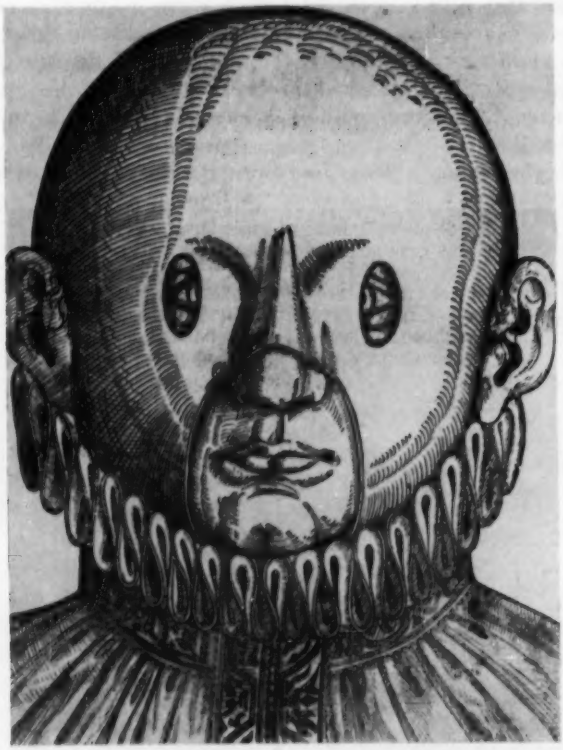

Fig. 3.—Head-hood with correspondingly arranged holes for strabismus.

some squints, Bartisch advocated purges, venesection, cupping, and blistering behind the ears with cantharides. A clever operative procedure for blepharophimosis consisting of the insertion of a lead plate after canthotomy through the outer canthus is described.

The third chapter deals with abnormalities of sight—how to avoid eyeglasses and disaccustom oneself from them. Bartisch felt that eyeglasses were detrimental. He could not conceive how an eye that already did not see well could see better with something in front of it. This is surprising.

since the usefulness of glasses had already been established.† Advocated instead are powders, eye-waters, and to stare or gaze at a chrysoprase stone (an apple-green variety of quartz). It is Hirschberg's conclusion that this is the weakest part of the book: "the obstinacy of the relatively uneducated handworker becomes obvious."[8] The most frequent cause of impaired sight mentioned is old age, "just as there are dark windows in old churches; still there are oldsters with good and youngsters with bad sight." Other causes listed are bad food, intracranial lesions, "fire-rays" (strong light and/or heat rays), the frequent reading of fine print, much bleeding, and much drinking. The conditions of hemeralopia (day blindness) and nyctalopia (night blindness) were well known to Bartisch. The chapter concludes with observations on snow-blindness.

Consideration of the subject of cataracts is next entertained, in Chapter 4. Conforming to the conception of the time, cataract is to Bartisch matter accumulating in the aqueous humor behind the iris and obstructing the pupil. It originates from sins, from changes in the brain, from bad blood, excessive dampness, from stomach troubles, poor food, too much wine, and trauma. A comprehensive list of etiological factors would be of prime

† Bernardus de Gordonio, in his "Lilium Medicinae," 1302. By the sixteenth century the use of spectacles with convex lenses was very popular. Pope Leo X wore a pair in 1517.

Fig. 4.—The operation of couching for cataract as practiced by Bartisch.

importance, since an adequate number becomes essential to satisfy every inquisitive patient.

Chapter 5 presents a review of *Star-Stechen,* or couching of cataract. Its description differs little from that of Celsus (25 B.C.-50 A.D.). The procedure is pictured in Fig. 4. Bartisch placed the needle temporally to the cornea, but firmly on the conjunctiva, and rotated the instrument into the interior of the eye. After making certain that the anterior chamber had been entered, he lifted the handle of the couching needle forward towards the forehead and pushed the cataract downwards. Here appears a uniquely frank passage: "There are among us, this very day, those who in a false manner announce themselves as oculists and eye-doctors. They couch the cataract in the market-place, in the wind outdoors; then allow the patient to leave like a hog from the trough. Naturally, all these people become blind." He further enters protests against these "bunglers" who following surgery demonstrate to the patient that a little sight has returned but after eight or ten days the eye becomes blind and remains severly damaged. "To couch the cataract properly, it must be done in the patient's home, allowing him plenty of rest in bed."

In the sixth chapter Bartisch reviews the subject of so-called "black cataract," which is not the nuclear cataract with the dark opacity familiar to modern ophthalmologists but instead a term synonymous with amaurosis. Gutta serena was the name given to this condition by the ancients—prob-

Fig. 5.—Application of the seton in epiphora.

ably original with the Arabians—supposing it to depend on a clear "liquid drop" fallen from the brain into the eye. If the patient is primarily blind from this affection, Bartisch continues, then he cannot in a lifetime, as far as is humanly possible, be cured. The principle cause, he states, is destruction of the "eye nerves," but now and then it happens to pregnant women, who after delivery begin to see again without the help of medications. This, of course, is the familiar blindness associated with toxemia of pregnancy.

The study of epiphora is attempted in Chapter 7. The important treatment is the seton (Fig. 5;) also the *Holztrank* (*decoctum lignorum*). Trachoma and blepharoadenitis were apparently one and the same to Bartisch.

The external tunics of the eye are next considered, in Chapter 8, including corneal dystrophies, opacities, and pterygium. He deprecates the common use of ferrous sulphate solution for corneal scars, which apparently was the vogue at the time, because as he points out the corneal pathology is in the deeper layers and cannot be reached by superficially applied medication.

In Chapter 9 are included growths of the eyelids, with a detailed discussion of malignancy, its complications, and possibilities for surgery. The external hordeolum was incised lengthwise; the internal, crosswise. The lacrimal fistula was split open, dilated with "gentian root," then cauterized or destroyed with heat. For long, pendulant, or heavy eyelids, a method was employed which involved pinching off a fold of skin with a clamp consisting of two movable blades, approximated by means of a screw

Fig. 6.—The use of the clamp instrument in lid surgery.

(Fig. 6). In ectropion, the excessive tissue was pierced with suture needles, lifted upward, and excised.

Chapter 10 deals with defects of the eyelashes—loss of lashes, pediculosis, and trichiasis. Pediculosis occurs only in unclean and unchaste people, but Bartisch continues that clean persons can also acquire the condition in bath houses, beds, at the barber. Among the remedies mentioned are powdered tin or mercury in lard. For trichiasis epilation was used with a specially designed forceps and sometimes cauterization with a caustic or excision of the lid margins, including the lashes.

Chapter 11 concerns injuries to the eye. Foreign bodies were washed out with a syringe, if possible. In the treatment of metallic splinters, a salve was used consisting of magnetic stone in harefat and laid over the eye like a plaster. Bartisch warns against laymen, "like blacksmiths and locksmiths" using sharp instruments, resulting in severe injuries, scars, and even cancer. In this chapter appears his famous description of enucleation with his razor-sharp spoon-shaped knives, with detailed instructions of the technique, as well as preoperative and postoperative care. Although an earlier recorded attempt at excision of the globe was made by Johann Lang, in 1555, his precise method was never determined.‡ Bartisch's operation was so dreadful that Guthrie in his work on the eye, published in

‡ Reference 1, p. 140.

Fig. 7.—Plate showing fruit-like growths which Bartisch describes. Also in the upper right corner are shown objects which festered from patients' eyes.

1823, mentions the fact that Bartolini endeavored to mitigate its severity by pulling out a cancerous eye by means of hooks, presumably a milder procedure, but this was followed in three days by the death of the patient in convulsions.[9]

The general subject of ocular pain is considered in Chapter 12. Bartisch simply divides the subject into (1) great eye-pain with discharge and wetness, (2) associated with much heat, (3) with great redness, (4) with edema.

Somewhat astonishing is the thirteenth chapter, in which injuries and defects arising from witchcraft, magic, fiends, and the work of the devil are described in detail. Bartisch testifies to many of these cases, which he claims he has witnessed himself. He states as a fact that some people had sustained injuries to their eyes and sight by witchcraft, describing small objects like clasps, bent pins, and buckle-pins which festered from patients' eyes. Hysteria undoubtedly existed then as now,[8] but it is of interest to note that Guillemeau's book in French, appearing two years later (1585) is not marred in this manner.[10] Bartisch continues: "also sometimes pieces of flesh grew out in no other form, but like natural pears and apples." These he proceeds to describe in detail (Fig. 7). Finally are recorded instructions under which of the twelve animal signs of heaven a good surgical prognosis could be assured (Fig. 8).

Fig. 8.—The Bartisch chart of the twelve heavenly signs consulted before performing surgery.

The last three chapters discuss hygiene, elaborating on skin conditions involving the region of the eyes, with the final chapter picturing apparatus used in making medications, solutions, and pharmaceutical preparations.

Comment

Bartisch was knee-deep in mysticism. Yet if the musty prejudices with which the superstitions of his time were intimately connected and the tight barriers of theology in which his calling was fettered are temporarily disregarded, he can be considered capable, honest, and industrious; a good observer; a skillful, enterprisingly bold surgeon. His book may be full of superstition and resembles in many respects an advertising medium, but it consists of truth as well as trash, wisdom as well as folly, sense as well as nonsense, sound instruction as well as ludicrous absurdity. The work takes a not unworthy place in the literature of ophthalmology and affords a comprehensive insight into sixteenth century medicine.[11]

The conditions then in Germany were no different from those all over Europe. Superstitions and mysticism reigned supreme, with the fantastic prejudices of ancient astrology playing a prominent role. Even Paré[12] urged that cataract surgery should be performed only at the time of the waning of the moon, at a time when there is no thunder or lightning in the sky, and when the sun is not in Aries, which is concerned with the head.[13] It is reasonable to assume that the medical profession might have kept the belief of witchcraft alive. What better way could there be in accounting for the etiology of numerous unknown diseases, which they could not cure nor rationally explain?[14] Moreover, the practice of the healing art had for a long time been considered a clerical right. The drawing of blood had been prohibited under pain of excommunication. Consequently, in many cases the practice of surgery was relegated to the laity, who did not care, and who performed their surgery in a mechanical manner, without thought about the art or its progress.[15] The disinclination of competent physicians to become interested in surgery of the eye had produced an unbearable situation, attracting ignorant and conscienceless charlatans, thus affecting the weal and woe of suffering humanity in a most lamentable manner.

So it is not without reason that the field was overrun by quacks. In his great treatise on surgery, published in the fifteenth century, Guy de Chauliac cautions that, because of the uncertainty of results, it would be better if all wise practitioners left cataract surgery to the itinerant physicians. Other medieval medical men expressed similar sentiments.[16]

Although Bartisch was not academically educated, still he seems to present a medical education as competent as his more highly learned colleagues. It is implied by some (Hirschberg, Burton Chance, and others) that Bartisch employed a scribe to write "Augendienst," because of its grandiose language, including Greek and Latin. There is no evidence that he was ever able to read any language except his own, but it is obvious that he had acquired much of the knowledge of the ancient physicians and that he knew Galen as well as his more fortunate contemporaries, who had the advantage of higher learning. His keen power of observation never deserted him, but unfortunately he was a child of his time and classified his

own views and observations unconditionally according to the then-existing age.

Only in ophthalmic surgery did he venture to follow his own methods and beliefs. If in certain surgical procedures he did not dare to withdraw from deep antiquity, as for example in the operation for cataract, yet he was well advanced in other operative procedures. For example, in his ptosis operation, the use of a clamp-instrument to aid in shortening the skin of the lids marked definite progress in lid surgery. This was held in esteem even until the nineteenth century, and such distinguished ophthalmologists as the Dutch eye physician Frederick Ruysch and the German oto-ophthalmologist Wilhelm Rau [17] held it not beneath their dignity to engage in a controversy about certain improvements of this apparatus.§ His dexterity and courage become evident in his phenomenal enucleation of the eyeball with all its associated soft parts, which he so skillfully executed, no doubt for the first time.

Of no small import was the Bartisch effort in the reformation of the traveling oculist and the elimination of the disgraceful conditions existing in the profession. In this he dreamed and wrought more nobly than many of his contemporaries.

Known almost exclusively by his "Augendienst," his life is to be found in his book. His mind was both scientific and speculative, but what he could not elucidate he covered with the inpenetrable darkness of the time. In summation of the life and work of George Bartisch the following Osler aphorism seems appropriate: "To have striven, to have made an effort, to have been true to certain ideals—this alone is worth the struggle."

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§ The instrument is described and illustrated as the forceps of Bartisch in Frick, G.: A Treatise on the Diseases of the Eye, Baltimore, 1823, p. 245 and Fig. 9 (the first American book on diseases of the eye). Also in Gibson, J. M.: A Condensation of Matter upon the Anatomy, Surgical Operations and Diseases of the Eye, Baltimore, 1832, p. 188 and Plate 10, Fig. 13, and it is mentioned again in Cooper, S: The First Lines of the Practice of Surgery, London, 1835, pp. 370-371.

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Meibomian Gland Tumors

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Meibomian gland tumors have been the subject of an uncommon degree of controversy concerning the question of their actual existence, the types of neoplasm that may develop, and the degree of malignancy that they may possess. Much of this controversy stemmed from the rarity of these tumors, which led to opinions on histology and clinical behavior based on single cases or very small series. Generalizations on incidence, classification, and malignancy have been of necessity based on compilations of previous reports, with the inherent limitations of this technique.

In spite of, or perhaps because of, the diversity of thought surrounding Meibomian tumors, numerous reports appeared in the medical literature following the original description of a Meibomian tumor by Baldauf [1] in 1870. Various authors considered all Meibomian tumors as adenomas,[2] while others stressed their malignant nature.[3] The existence of both adenomas and carcinomas was suggested by significant differences in the clinical reports,[4] and this division of Meibomian tumors into adenoma and adenocarcinoma is employed in several contemporary textbooks.* However, classification of these tumors has remained controversial † because of their unique histological features and the difficulty encountered in correlating histopathology with malignant potential.

Generally speaking, benign Meibomian tumors are diagnosed only infrequently, and so age and sex distribution have not been determined. Benign growth may attain considerable size and assume the form of a hard lobulated mass in the tarsal portion of the lid. Treatment by surgical excision is advisable, although recurrences frequently develop if excision is not complete.[5]

Malignant Meibomian tumors have been noted more frequently, and in 1950 the total of Meibomian carcinomas in the world literature was 97.[9] Since that publication, Murrah,[10] Kamel,[11] Kennedy and King,[12] and Hartz [13] have reported single cases, while Spaeth [14] has cited three cases of "primary adenocarcinoma of the tarsus." No exact enumeration of the reported cases is possible, because of differences in terminology, the diverse criteria for diagnosis, and incomplete breakdown of reported material.[15] Moreover, a simple listing of reported cases does not contribute more than a general impression of the incidence of these tumors.

The question of geographic incidence deserves consideration from the practical standpoint of diagnosis and with a view of eliciting possible etiologic factors. In a recent paper, Hartz [13] called attention to the relatively large number of Meibomian carcinomas reported from a single city in Indonesia, but diagnosis in these cases must be accepted with reservation, and certainly

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* References 5 and 6.
† References 7-9.

no local predisposing or precipitating factor has been demonstrated. Review of the world's literature does reveal reports of malignant Meibomian gland tumors encountered in North America, South America,[13] Europe, Africa,‡ Asia,[17] and the Indonesia area.[18] Consequently, the only general statement on geographic incidence warrented at this time is the conclusion that no major area of the globe is free from this type of neoplasm.

Meibomian carcinomas occur in both sexes with almost equal frequency according to some authors,§ though others ‖ have stated that females are more frequently afflicted. Usually these tumors develop in middle life, and, as with many other neoplasms, the age between 40 and 80 is considered most vulnerable. Exceptions occur, and H. Knapp[20] reported a case which developed in a 3½-year-old child, while another case of Meibomian carcinoma occurred in an 11-year-old patient.[21]

The clinical picture of Meibomian carcinoma is focused about the growth of a painless firm nodule that develops more frequently in the upper than in the lower eyelid.¶ Multiple Meibomian carcinomas have been reported in a single lid,[22] and the malignant potential of these tumors is demonstrated by both extension and metastasis. Typically, local extension is directed toward the orbit, and adhesion between the involved lid and the cornea has occurred.[3] More extensive orbital involvement # has produced massive tumefaction resulting in a fatal termination.

Metastasis of Meibomian carcinoma is generally along the path of lymphatic drainage. It is significant that regional node involvement may be detected at the time the primary malignancy is diagnosed[11] or it may be discerned clinically at a later date. The patient reported by A. Knapp* had excision of involved preauricular nodes eight months after removal of a recurrent Meibomian carcinoma, while Hagedoorn[19] noted an interval of four years between resection of the Meibomian carcinoma and excision of regional nodes containing metastatic tumor. Most frequently involved are the preauricular or parotid lymph nodes, although the submaxillary nodes and the entire cervical chain may contain metastatic tumor.† Also reported is a metastatic lesion to the lip with extension to the nose and malar bone,[14] and death has resulted from multiple metastatic lesions,‡ including spread to the liver.[26]

Therapy of Meibomian carcinomas has, in general, paralleled methods devised for other neoplasms of the skin and its appendages. Surgical attack on the eyelid tumor has been the most frequent mode of therapy. Numerous cases have demonstrated that incising, curetting, cauterizing, or incompletely excising these tumors will result in recurrence, often with growth at a seemingly accelerated rate.§ Consequently, wide excision of the primary lid tumor is the favored treatment, with closure by simple approximation of the incised edges or plastic reconstruction.

‡ References 11, 15, and 16.
§ References 4 and 19.
‖ References 5 and 12.
¶ References 4 and 19.
# References 17, 18, 23, and 24.
* Knapp, A., in discussion on O'Brien.[25]
† References 14, 19, and 25.
‡ Knapp, A., in discussion on O'Brien.[25]
§ References 5 and 27.

Treatment of orbital extension necessitated exenteration of the orbit in at least nine patients reported in the literature,‖ and metastasis to regional lymphatics has made node resection mandatory.

Radiation therapy for Meibomian carcinoma employing radium application and the implantation of radium seeds has been generally unsuccessful.¶ The experience with x-ray therapy has been decidely more promising, though no five-year cure has been reported.#

Evaluation of the relative malignancy of Meibomian carcinoma presents a problem that cannot be adequately resolved on the basis of reports now available in the literature. Isolated tumors were usually reported within a short time after diagnosis had been made and therapy undertaken. Consequently, the ultimate result of the case is not known except when rapid progression and a fatal outcome terminated the course. Spaeth [14] noted one death in a series of three cases and stated that adenocarcinoma arising in the tarsus, i.e., of Meibomian gland origin, is the most malignant of all the epithelial-cell tumors of the eye. These reports of fatal termination combine with the uncertainty of outcome surrounding the majority of cases to imply a distinctly unfavorable prognosis for Meibomian carcinoma.

The investigation reported in this paper is based on material obtained from the pathology collection of the Institute of Ophthalmology supplemented by specimens studied through the courtesy of the Armed Forces Institute of Pathology. This study was undertaken to develop a classification of Meibomian gland tumors, to determine histologic criteria for their diagnosis, and to correlate the histologic and clinical features of these tumors. However, interpretations and conclusions pertaining to neoplasms of the Meibomian gland must be made against a background of normal Meibomian gland development, anatomy, and physiology.

The Meibomian glands develop as an ectodermal ingrowth from the inner parts of the fused lid margins during the fourth month (80 mm. stage) of intrauterine life.[29] They form a single row of parallel vertically arranged glandular structures occupying the tarsal plate of both the upper and lower lid. Wolff [30] states that there are about 25 glands in the upper lid and 20 in the lower, though other authors give a somewhat higher estimate.[5] Each gland is composed of a linear central tube, or duct, which emerges on the lid margin between the intermarginal sulcus and the posterior marginal border. Into the sides of this central tube open as many as 30 or 40 small ducts leading to rounded simple or branched alveoli. The duct of the gland is lined by stratified squamous epithelium, while the secretory alveoli, or acini, consist of a basement membrane separating the supportive elements from a single layer of small flat undifferentiated cells. Centrally in the acinus are the larger, more mature cells that assume a polyhedral form and contain many fat droplets (Fig. 1). This lipid is responsible for the characteristic yellow color associated with Meibomian glands and is disclosed by special fat stains or demonstrated by the coarse vacuoles that remain in the tissue specimen after fat dissolution. Culmination of the secretory process occurs when the nuclei of the large central cells degenerate

‖ References 5, 17, and 19.

¶ References 22 and 28; Knapp, A., in discussion on O'Brien.[28]

References 16 and 24.

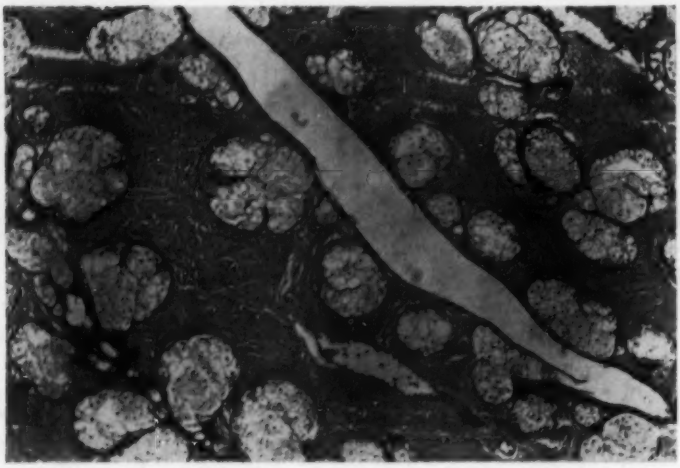

Fig. 1.—Normal Meibomian gland histology. Hematoxylin and eosin; reduced from mag. × 110.

and the cells break down—a holocrine type of secretion—to release a mixture of cell remnants, fat, fatty acids, and cholesterol. Replacement of the secretory cells is accomplished to some extent by mitosis of cells in the periphery of the acinus but principally by mitosis of duct cells located near the mouth of the acinus. The duct cells then become incorporated in the secretory alveolus and undergo the characteristic maturation of sebaceous elements.*

With this introductory consideration of Meibomian gland anatomy, attention may be given to tumors arising from these structures. In my opinion, origin of the tumor from Meibomian gland is established when two criteria are fulfilled. First, the tumor must arise in the sharply demarcated tarsal portion of the lid and show either direct continuity with a Meibomian gland or conspicuous proximity between gland and tumor. Second, there must be a histologic resemblance between the cells of the normal gland and the aberrant cells of the tumor. With use of these criteria of Meibomian gland origin, a series of 21 cases was assembled. This group may be divided into benign and malignant types and further classified as noted in the Table. Nineteen of these tumors are reported here for the first time. One case of carcinoma was previously described by Dr. M. C. Wheeler [33] and Dr. A. B. Reese,[27] and another case of carcinoma was noted by Dr. W. F. Murrah.[10]

Classification of Meibomian Gland Tumors

	Number of Specimens
Benign	
Hyperplasia	1
Adenoma	3
Hamartoma	1
Malignant	
Carcinoma	16
	21

* References 31 and 32.

This classification is based on over-all organization of the tumor and its cytologic characteristics. Both acinar and duct portions of the gland participate in the neoplasia, and there is no evidence to suggest that specific tumors arise from duct as opposed to acinar portions of the gland. On the contrary, the similar embryological development and the normal interchange of cells between duct and the acinus makes it reasonable to expect that both portions of the gland possess equal neoplastic potential.

The benign Meibomian tumors are classified as hyperplasia, adenoma, or hamartoma. Such a classification is essential to orderly evaluation, but it is presented more to emphasize the difference in organization of these benign tumors than it is intended to serve as the basis of a dogmatic and absolute division. A sharp splitting or division of these tumors is not feasible when it is apparent that gradations of structure and activity may arise to compromise the most careful classification.

The benign tumor most closely related to the normal gland is essentially a hyperplasia. To consider hyperplasia as a form of tumor is somewhat unique in pathology. However, as applied to sebaceous glands it is generally accepted that there is a form of overgrowth and multiplication which approaches a neoplastic grade.†

In this form of tumor there is a localized overgrowth with no disturbance in the orderly parallel arrangement of the glands, and the normal relationship between duct and secretory acinus is maintained. However, the number of acini surrounding each duct is greatly increased and there is a true hyperplasia involving both ducts and acini (Fig. 2). The ducts are lined

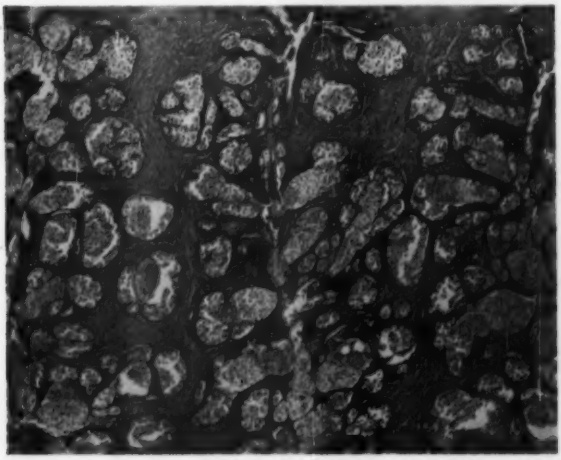

Fig. 2.—Meibomian gland hyperplasia. Orderly overgrowth with an increase in cell components of acini and ducts. A.F.I.P. No. 514703. Hematoxylin and eosin; reduced from mag. × 48.

by an epithelial layer increased to six or seven cells in thickness, and some duct cells contain numerous lipid vacuoles in their cytoplasm. In the acini, the hyperplasia is demonstrated by an increase in the undifferentiated cells lining the periphery. Despite this significant increase in cellular components, the process is uniform and orderly and the fibrous structure of the tarsal plate is free of inflammation and necrosis (Fig. 3).

† References 34-36.

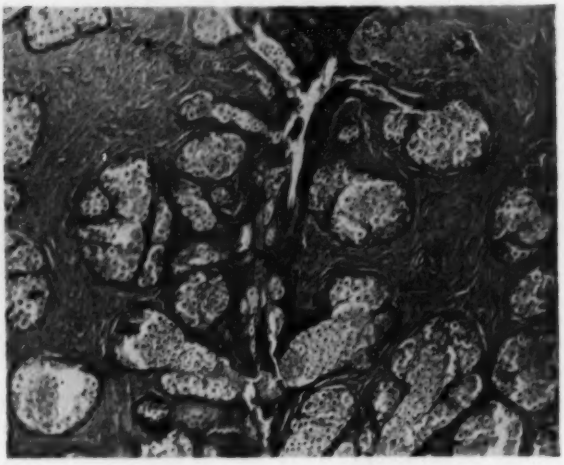

Fig. 3.—Meibomian gland hyperplasia. Higher magnification of Figure 2 to show cell differentiation. A.F.I.P. No. 514703. Hematoxylin and eosin; reduced from mag. × 75.

The true adenoma is distinguished from this primarily hyperplastic lesion by its disorganization and loss of pattern.[37] In the true adenoma, acinar organization is retained but there is no vestige of parallel linear organization and no central duct structure is present (Fig. 4). Epithelial-cell matura-

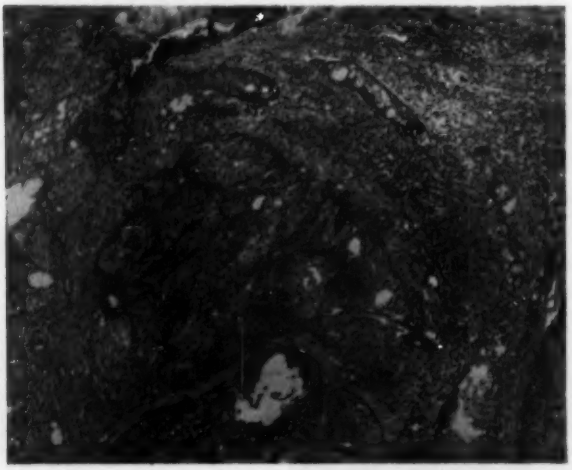

Fig. 4.—Meibomian gland adenoma. Acinar organization is retained, but no central duct or parallel linear pattern is present. A.F.I.P. No. 312566. Hematoxylin and eosin; reduced from mag. × 75.

tion is essentially orderly, although growth is less restrained. The undifferentiated germinal layer is more prominent and may consist of three or four layers of spindle cells arranged perpendicular to rather than parallel to the basement membrane. A few mitotic figures are discernible, and all stages of transition between undifferentiated and mature sebaceous cells are present (Fig. 5). Clusters of cells or acini are typical in form and generally larger than normal. These contain varying proportions of mature and immature cells. A preponderance of small immature cells produces a solid portion, whereas a majority of mature sebaceous cells more closely simulates normal acinar organization (Fig. 6). The stroma is composed

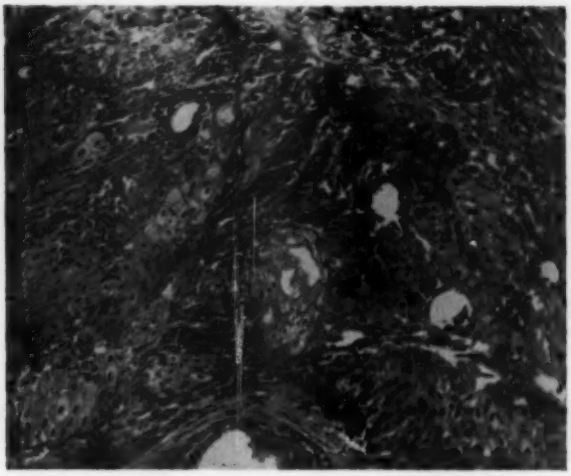

Fig. 5.—Meibomian gland adenoma. Epithelial-cell maturation is less restrained, and undifferentiated spindle-shaped cells are prominent. A.F.I.P. No. 312566. Hematoxylin and eosin; reduced from mag. × 160.

of fibrous tissue containing vascular structures and a minimal to moderate infiltration with the cells of chronic inflammation. Meibomian adenomas are sharply localized masses that are space-occupying. Therefore, as growth occurs, they compress and displace adjacent structures without showing any tendency to infiltration (Fig. 7).

The third type of benign tumor is classified as a hamartoma. This term, derived from the Greek word meaning "to fail or miss," was introduced by Albrecht as a designation for tumor-like malformations showing a faulty mixture of the normal components of the organ in which they occur.[38] In this general sense, all benign Meibomian gland tumors may be be considered to be hamartomas. However, as applied here, the term hamartoma is used to denote those benign Meibomian tumors in which both the parallel linear arrangement and the tendency to form acini have been

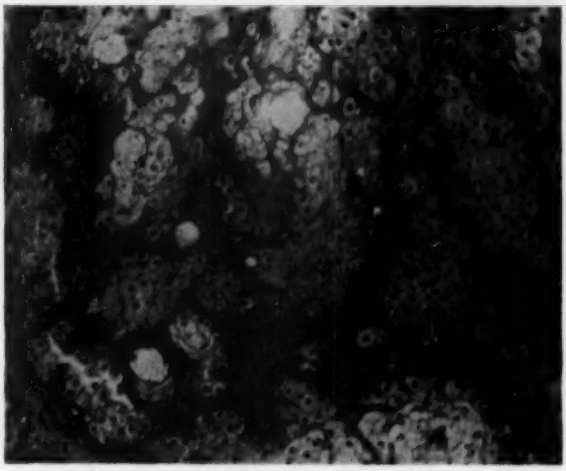

Fig. 6.—Meibomian gland adenoma demonstrating acini containing a preponderance of mature sebaceous cells. A.F.I.P. No. 209672. Hematoxylin and eosin; reduced from mag. × 160.

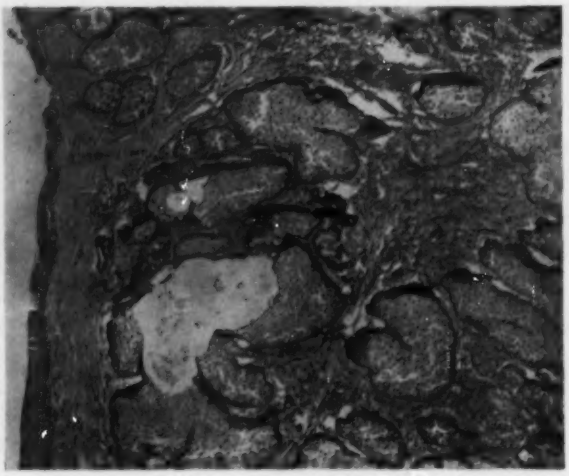

Fig. 7.—Meibomian gland adenoma. Conjunctiva, orbicularis muscle, and normal Meibomian elements are displaced by the expanding tumor mass. A.F.I.P. No. 501759. Hematoxylin and eosin; reduced from mag. × 48.

disrupted. Specifically, the epithelial components of this tumor type are arranged in sharply deliniated cords, strands, and masses with several interspersed cystic structures (Fig. 8). These epithelial masses and cords contain large numbers of rather small cells with darkly staining nuclei and basophilic cytoplasm. There is palisading of the nuclei at the periphery of the cell clusters, and dispersed throughout these epithelial columns and masses are numerous clusters of mature sebaceous-type cells. Cystic areas, which are present in random distribution, are lined by sebaceous epithelium (Fig. 9). The stroma of this hamartoma is composed of a loose form of connective

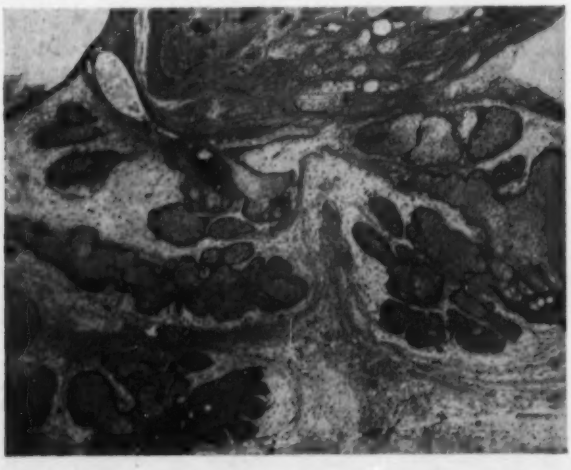

Fig. 8.—Meibomian gland hamartoma. Cords and masses of epithelial cells are surrounded by a distinctive stroma. A.F.I.P. No. 644492. Hematoxylin and eosin; reduced from mag. × 48.

tissue surrounding the epithelial masses with intermingled dense bands of collagen fibers. The tumor is clearly circumscribed, and inflammatory reaction is insignificant. This unique epithelial arrangement and supportive structure contrast sharply with the normal gland and tarsus and indicate the pleomorphism that may be encountered with hamartomas.

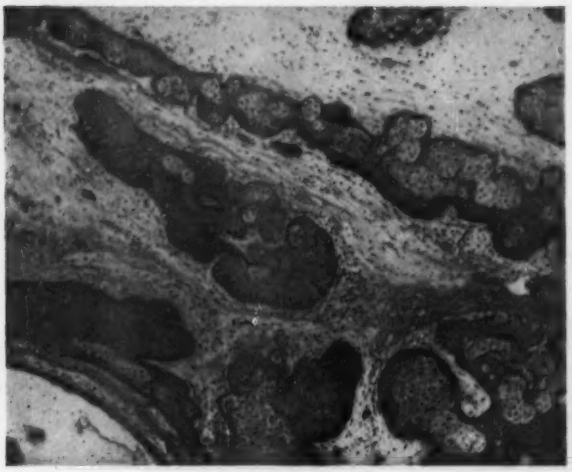

Fig. 9.—Meibomian gland hamartoma. Epithelial-cell cords contain numerous clusters of mature sebaceous-type cells. A.F.I.P. No. 644492. Hematoxylin and eosin; reduced from mag. × 75.

To summarize clinical features, the benign Meibomian tumors may be considered as a group because behavior of these tumor types is similar. The available data on these five cases reveals that these tumors developed in both sexes and that the average age of the patient at the time of treatment was 62 years, with a range from 49 to 74 years. The upper eyelid was the tumor source more frequently than the lower—a finding consistent with the fact that there are more Meibomian glands in the upper than in the lower eyelid.

These benign tumors began insidiously with the painless development of a mass in the tarsal portion of the lid. The lesions were nontender nodular firm pink-white masses with yellow foci. They gradually increased in size and usually produced thickening and distortion of the lid. One tumor presented as a pedunculated lesion elevating the tarsal conjunctiva, and another became large enough to produce a purely mechanical ptosis of the upper lid. Hyperemia and ulceration of the overlying skin and conjunctiva occurred, although ulceration was relatively late in development.

Treatment of every benign tumor was surgical excision. Follow-up of these patients has been attempted by the Armed Forces Institute of Pathology, but the only available information indicates that one tumor (classified as a hamartoma in this series) has been followed without recurrence for about two years. From all indications, the only sequelae to be expected following resection of a benign tumor would be local recurrence after incomplete excision. The basic relationship between benign and malignant Meibomian gland tumors is not known, and although malignant degeneration of a benign tumor is a possibility it has never been demonstrated.

The malignant Meibomian gland tumors are termed carcinomas. Adenocarcinoma is the name usually given to these lesions, and against this term there can be no strong objection. However, the designation of Meibomian gland carcinoma is equally descriptive, simpler, and more applicable to malignant tumors showing no trace of glandular organization.

There is unequivocal justification for considering these tumors malignant on the basis of morphological changes and the proof of a metastatic potential.

Prominent features in their histologic diagnosis are the over-all organization of the tumor cells into masses, the characteristics of the individual malignant cells, and the relationship between the tumor and adjacent structures.

The organization of cell clusters is an important feature in the identification of these carcinomas. Cells may form giant acini, extensive sheets, or thick cords or they may be scattered in a diffuse form. These patterns represent variations in histologic appearance without fundamental significance in terms of origin or prognosis, and frequently several forms are combined in a single tumor. The acinar form is by far the commonest,

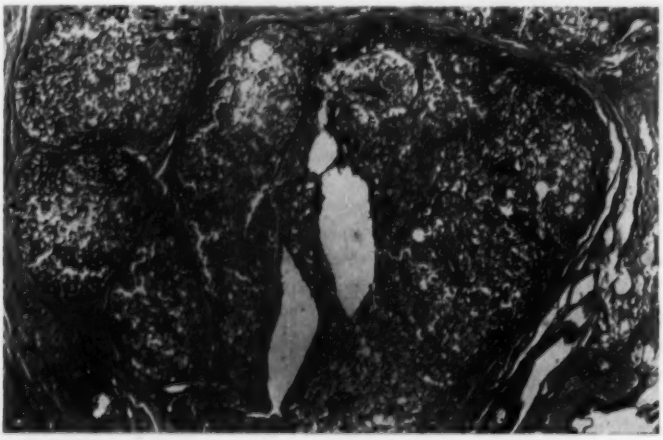

Fig. 10.—Meibomian gland carcinoma with prominent acinar pattern. Hematoxylin and eosin; reduced from mag. × 110.

and in this type the cells aggregate into round or oval masses of variable and often gigantic size. These masses are surrounded by a basement membrane and a system of supporting tissue, with thin extensions of this supportive structure extending toward the center of the acini and producing a form of branching or lobulation (Fig. 10). Though this arrangement of cell clusters bears closer resemblance to the normal acini than to the duct of the gland, an entirely analogous process involves the duct structures, even to their point of union with the eyelid margin (Fig. 11). Polarity of these tumors is not uniform. However, the less-differentiated cells are usually at the periphery of the acinus or along the thin fibrous septa, while the cells with more vacuolated cytoplasm are more central, and in the axial position a variable amount of fat and cell breakdown products is accumulated. Special stains portray fat as red-colored material. These stains reveal tremendous quantities of lipid in the vacuolated cells and the central area of breakdown products (Fig. 12).

Extensive sheets of cells are encountered as another variation of tumor organization. In this variation the stroma is reduced to a series of fine connective tissue septa. The less-differentiated cells are adjacent to these septa, and more mature cells are located in the central portion of the cell mass (Fig. 13). Thus these fibrous strands are comparable to the septa

Fig. 12.—Meibomian gland carcinoma. Specific stain for fat reveals tremendous quantities of red colored lipid in the vacuolated cells and in the central area of breakdown products. AFIP No. 541358. Specific fat stain: X 60.

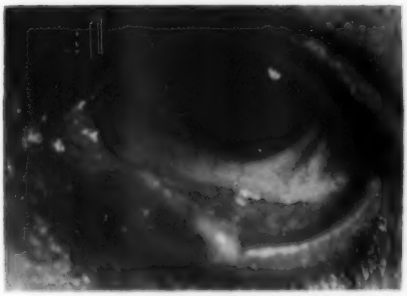

Fig. 25.—Meibomian gland carcinoma. Clinical appearance demonstrating tumor appearance and prominent nutrient-type vessels.

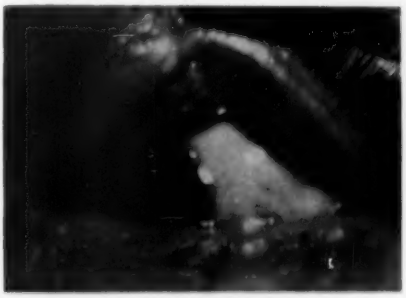

Fig. 26.—Meibomian gland carcinoma. Clinical appearance with characteristic lobulation and yellow-white color.

Fig. 11.—Meibomian carcinoma involving both the acinar and duct portions of the gland. The malignant process extends along the duct to the eyelid margin. Hematoxylin and eosin; reduced from mag. × 110.

producing lobulation in the normal gland and the acinar type of carcinoma. The appearance of this tumor type may be understood by considering it as a giant acinar form that is lacking a sharp connective tissue outline at its periphery.

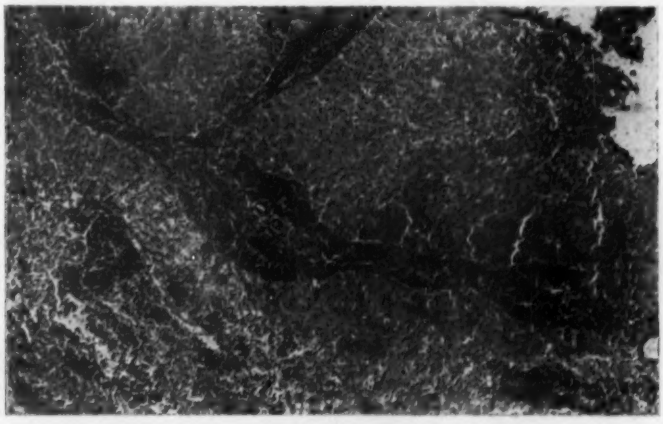

Fig. 13.—Meibomian gland carcinoma demonstrating fine connective tissue septa and extensive sheets of cells. Hematoxylin and eosin; reduced from mag. × 110.

A third variation in gross organization is the appearance of solid cords or strands of neoplastic cells (Fig. 14). This may be a prominent feature, and these cords resemble the organization encountered in basal-cell carcinoma. Significantly, in this series of tumors, cell columns have always been associated with at least a limited portion of the tumor demonstrating true acinar organization.

The fourth and final variation is truly different from the types previously considered. In this form, there is a diffuse haphazard spread of neoplastic cells without regard for acinar structure or column formation. The fibrous tissue of the lid divides the tumor into numerous irregular small cell clusters, and only the typical anaplastic Meibomian cytology provides the diagnosis (Fig. 15).

From this enumeration of the gross variations encountered in these tumors, it is apparent that the fibrous stroma must undergo considerable

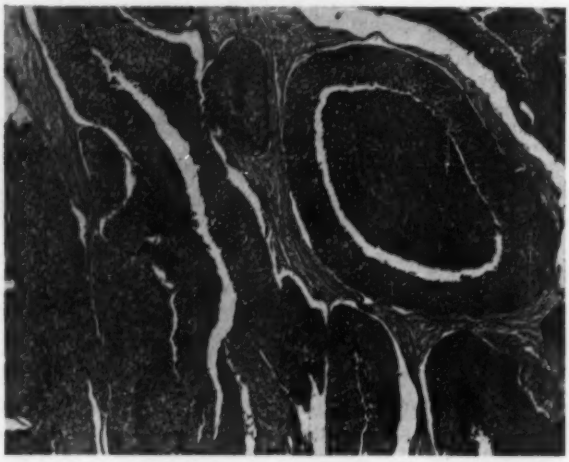

Fig. 14.—Meibomian gland carcinoma with solid cords of neoplastic cells. A.F.I.P. No. 541358. Hematoxylin and eosin; reduced from mag. × 48.

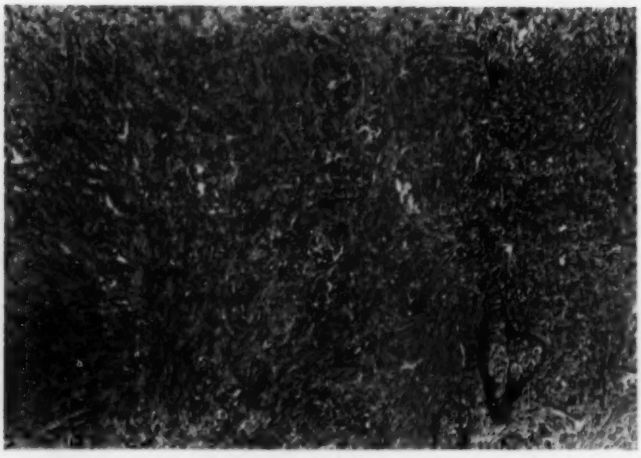

Fig. 15.—Meibomian gland carcinoma. Small clusters of malignant meibomian cells are spread diffusely. Hematoxylin and eosin; reduced from mag. × 110.

alteration to conform with the differences in epithelial organization. This stroma is composed of solid-appearing bundles of connective tissue containing a moderate number of blood capillaries and larger vessels. Inflammatory response in the stroma is the exception rather than the rule and is usually associated with ulceration or a history of previous surgical intervention.

Histologic characteristics of the individual tumor cells are of prime importance in establishing the diagnosis of Meibomian carcinoma. Carcinoma is indicated by the loss of orderly cell differentiation and the evidence of excessive mitotic activity. The bulk of the tumor is composed of abnormal cells exhibiting all degrees of differentiation. Relatively immature cells are frequently spindle-shaped and arranged in masses to form swirls of cells. The nuclei of these abnormal cells are fusiform and demonstrate a wide variation in size and staining properties. The cytoplasm is scanty, but most of these cells contain one or more vacuoles (Fig. 16).

The major portion of the tumors is composed of larger, more differentiated cells that are rounded or polyhedral. The nuclei of these cells are vesicular, with granular basophilic material and prominent nucleoli. Many round vacuoles are present in the cytoplasm as evidence of fat removed from the cell during the preparation of the specimen (Fig. 17). The largest cells may show degenerative changes in the nucleus, abnormally large vacuoles in the cytoplasm, and even rupture of the cell wall. Extensive cell breakdown results in large areas located in the center of the acinus that contain amorphous cell debris and fat (Fig. 18).

An important feature of these tumors is the great number of mitotic figures present in the neoplastic cells. Mitosis is only rarely seen in the normal gland and is occasionally present in the benign tumors, but all carcinomas contain large numbers of dividing cells, indicative of rapid growth. These mitotic figures are seen in cells with partially vacuolated cytoplasm

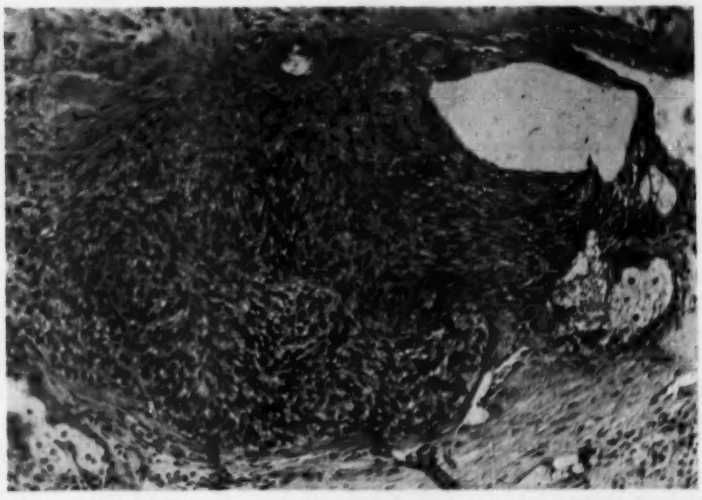

Fig. 16.—Meibomian gland carcinoma. Small spindle-shaped cells with vacuolated cytoplasm are arranged in swirls and masses. Hematoxylin and eosin; reduced from mag. × 220.

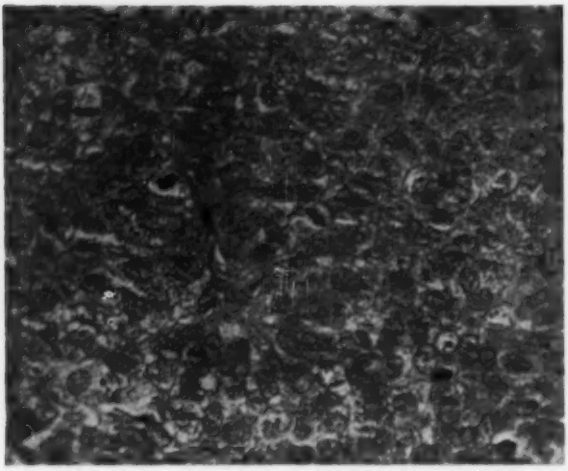

Fig. 17.—Meibomian gland carcinoma. Larger, more differentiated cells with vesicular nuclei and prominent nucleoli form the major cell type of meibomian carcinoma. A.F.I.P. No. 294681. Hematoxylin and eosin; reduced from mag. × 1110.

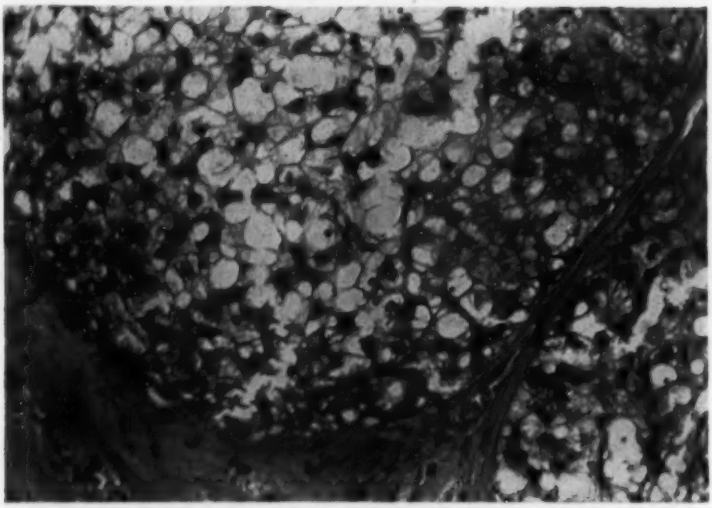

Fig. 18.—Meibomian gland carcinoma. Degenerative changes take place in the large cells located near the center of the acinus. Hematoxylin and eosin; reduced from mag. × 500.

and are found at any stage of differentiation prior to the degenerative process. So numerous are these multiplying cells that a malignant process is certainly evident (Fig. 19).

Evaluation of a malignant tumor is not complete unless attention is given to the relationship between the tumor and adjacent structures. Of interest is a form of cystic degeneration that develops in the Meibomian glands adjacent to or proximal to the actual neoplasm. Undoubtedly these cysts arise when obstruction of the duct produces an accumulation of retained secretion which forces an increase in acinar size until the pressure of the surrounding tarsus inhibits cell differentiation. Formed in this process are a number of large rounded spaces containing a slight amount of cell break-

down products. These spaces are arranged in the linear fashion characteristic of normal Meibomian glands and are lined by two or three layers of small flat cells (Fig. 20). This process of cystic degeneration is not specific for

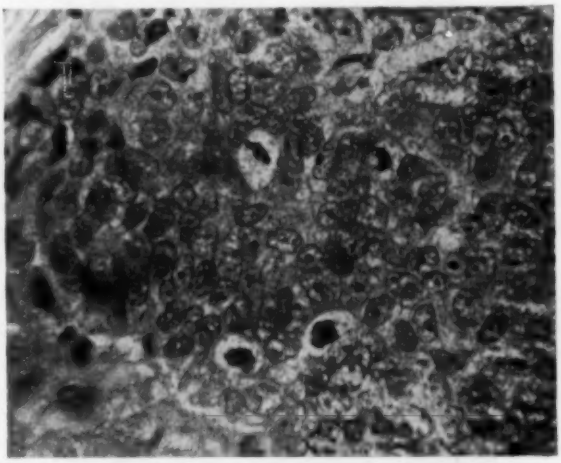

Fig. 19.—Meibomian gland carcinoma. Large numbers of mitotic cells indicate excessive cell activity. A.F.I.P. No. 294681. Hematoxylin and eosin; reduced from mag. × 800; oil.

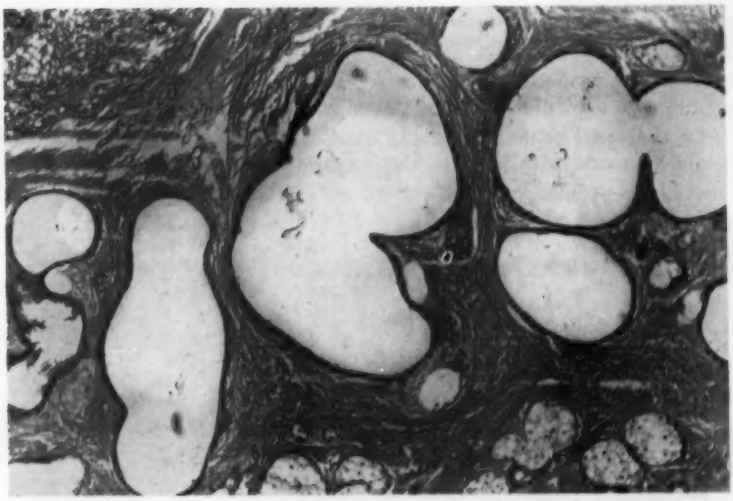

Fig. 20.—Cystic degeneration of the Meibomian gland. This nonspecific change develops in Meibomian glands adjacent to or proximal to the actual neoplasm and is secondary to duct obstruction. Hematoxylin and eosin; reduced from mag. × 110.

Meibomian tumors, because it is seen in basal-cell involvement of the lid margin and probably follows surgical procedures such as those for lid adhesions. Because of the appreciable length of Meibomian glands, cysts may occur at a distance from the tumor, and the presence of these cysts at the edge of a section does not indicate incomplete excision.

Important questions such as relative malignancy and the advisability of local excision are dependent upon the local invasiveness of the tumor. This

study strongly suggests that even the malignant Meibomian tumors grow in an expansile fashion without a predilection for invading normal tissue. The pressure of expansile growth bows forward the orbicularis and anterior lid structures to form a pseudocapsule for the tumor (Fig. 21). The diffuse

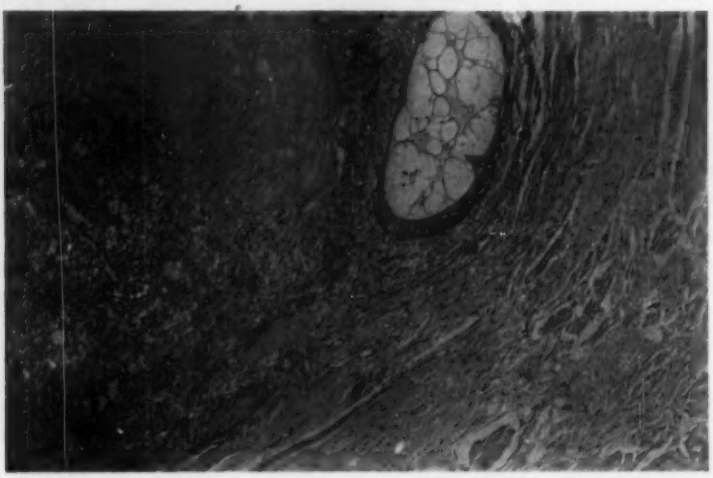

Fig. 21.—Meibomian gland carcinoma demonstrating expansile growth with formation of a pseudocapsule. Hematoxylin and eosin; reduced from mag. × 110.

form of tumor growth has a greater local invasiveness, as seen by the involvement of orbicularis fibers, but even here a rather sharp line may be drawn at the limit of the tumor (Fig. 22). Skin and conjunctiva undergo appreciable distortion because of this expanding mass, but ulceration, shown here involving the conjunctiva, occurs only when local growth is relatively advanced.

Fig. 22.—Meibomian gland carcinoma. The diffuse form of tumor involves orbicularis fibers but remains restricted. Hematoxylin and eosin; reduced from mag. × 110.

One metastatic lesion was encountered in this series. The primary carcinoma assumed the typical acinar form with malignant cytology (Fig. 23). The metastatic lesion developed in the ipsilateral preauricular lymph node

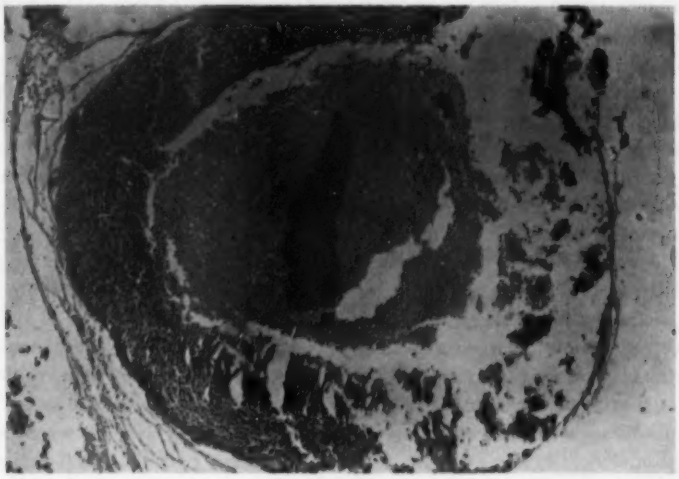

Fig. 23.—Meibomian gland carcinoma. The histopathology of this primary tumor is typical of the acinar form of meibomian carcinoma. Hematoxylin and eosin; reduced from mag. × 110.

and demonstrated acinar formation with cytology comparable to that of the primary growth (Fig. 24). No extension of Meibomian carcinoma into the orbit was encountered in this series.

Clinical features associated with the 16 cases of Meibomian carcinoma merit consideration. Females were affected more frequently than males in the ratio of 11:4, with 1 unknown. The average age of these patients at the time of excision was 57 years, with a range from 20 to 84 years. The upper lid was involved nine times, and the lower lid was the site in seven patients. Again, this predilection for

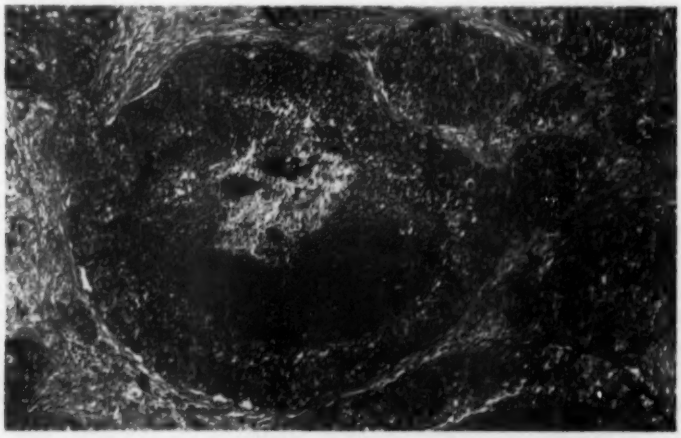

Fig. 24.—Metastatic Meibomian gland carcinoma. This metastasis in the preauricular lymph node demonstrates acinar formation and cytology comparable with the primary growth. See Figure 23. Hematoxylin and eosin; reduced from mag. × 110.

the upper lid is consistent with the greater number of Meibomian glands in the upper than in the lower lid.

Onset of Meibomian carcinoma was dominated by the insidious development of a firm painless nodule in the tarsal portion of the lid. In its early stages, skin rolled freely over the lesion and the lid margin could be either spared or involved. Overlying skin and conjunctiva were stretched and prominent; grossly visible nutrient-type vessels frequently coursed over the tumor (Fig. 25). As growth continued, the tumor became nodular or lobulated and assumed a yellow-white color. At this advanced stage the lid margin was almost invariably fused with both the tarsus and the tumor, and local atrophy with loss of cilia was encountered (Fig. 26). The tumor was capable of eroding skin or conjuntiva, with resultant ulceration on the lid margin or into the conjunctival sac, and in one case a fungating mass developed from the conjunctival surface of the lid. More frequently, the late manifestation was gross distortion of the lid, including eversion of the punctum, ectropion, or a mechanical ptosis.

Subjective symptoms were generally very mild or even entirely absent. Pain was mentioned in only two cases, and epiphora was encountered in two others. It is obvious that cosmetic considerations or simple awareness of the mass forced the patients to seek medical attention in most cases. The period between onset of the growth and definitive treatment is known in all but two cases and varied from five months to seven years, with an average of three years.

Confirmation of the difficulties that this diagnosis may present is obtained from the fact that only 4 of the 16 patients had definitive therapy as a primary procedure. On the 12 other patients, a total of 22 surgical procedures were performed and 2 of the patients received x-ray therapy before adequate measures were undertaken.

The definitive therapy utilized in every case of Meibomian carcinoma in this series was surgical excision. Local considerations such as the size and location of the growth dictated the form of plastic reconstruction utilized, and various surgical techniques such as those described by Dr. J. M. Wheeler ‡ and Dr. W. L. Hughes [41] were applied, with generally excellent results.

Treatment of the metastatic lesion in this series warrants a detailed report, because unequivocal cure of a patient with disseminated disease is unique in the accumulated experience with Meibomian carcinoma. This patient, reported through the courtesy of Dr. J. H. Dunnington, presented with a right upper lid tumor and an enlarged palpable right preauricular node. The primary lesion and the preauricular node were excised simultaneously, and histologic study demonstrated Meibomian carcinoma in both specimens.

The patient was referred for radiotherapy,§ and a total of 1625 r (air) in 16 days (200 kv., HVL 2 mm. Cu, TSD 50 cm.) was given through an 8 × 10 cm. lateral port over the right parotid area. During this phase of treatment, the region of the preauricular node dissection was shielded. A node 2 cm. in diameter located at the angle of the right mandible was further treated with 6 and 4 cm. diameter cones to a tissue dose at 2 cm. depth of 5750 r in 41 days. Six months later the right preauricular region (previously shielded) was given a tissue dose at 1 cm. depth of 5400 r in 43 days (130 kv., estimated HVL 4 mm. Al, TSD 50

‡ References 39 and 40.

§ Dr. George R. Merriam Jr. and Dr. Kent Ellis summarized the data pertaining to radiotherapy.

cm.). With use of similar factors, the area of the right external canthus received a tissue dose at 0.5 cm. depth of 5900 r in 30 days through a small shielded port.

Follow-up information concerning the entire group of patients with Meibomian carcinoma was assembled from hospital records, the office files of attending physicians at the Institute of Ophthalmology, letters to patients, and the standard follow-up procedure utilized by the Armed Forces Institute of Pathology. Nine patients were followed for less than one year; one patient had surgery less than a year ago, and another died of intercurrent disease 10 days after surgery. Consequently, only five patients were followed for a period of greater than one year. These patients were well 2 years 8 months, 6 years, 7 years, 10 years,and 15 years after resection of the tumor. The 15-year follow-up refers to the patient with metastatic disease previously discussed. Not a single recurrence or extension of Meibomian carcinoma is known to have occurred following definitive surgery.

Although this follow-up is far from complete, the presence of several patients surviving and without recurrence for a period of greater than five years conclusively demonstrates that this type of carcinoma can be successfully combated by methods now available and suggests that the prognosis is more favorable than the literature would indicate.

The most advisable therapy of Meibomian carcinoma would seem to be adequate surgical excision of the primary neoplasm in the lid. Despite the definite presence of a pseudocapsule in several specimens, excision of the full lid thickness is favored because infiltration of the anterior lid layers can occur and resection of the full lid thickness does not appreciably impair the ultimate cosmetic result. If regional nodes are enlarged at the time the diagnosis of carcinoma is established, these nodes should be excised and studied histologically for evidence of metastatic tumor. The presence of metastatic lesions is an indication for radiotherapy with adjustment of technique in accordance with the path of probable tumor spread. Whether or not enlarged regional nodes are present at the time of lid surgery, the patient should be observed for a period of at least five years. Local recurrence of the lid tumor and the delayed appearance of metastatic lesions are ever-present possibilities. Prophylactic excision of regional and cervical lymph nodes is not advocated, because the experience of this series indicates that an overwhelming amount of unnecessary surgery would be performed with its attendant morbidity and potential mortality. Furthermore, prompt and vigorous therapy directed against the metastatic lesion has been shown to be capable of controlling the disease.

In this series there has been no experience with extension of Meibomian carcinoma into the orbit. However, the use of even radical orbital surgery as a life-saving measure would seem justified.

The role of x-ray therapy in the treatment of primary Meibomian carcinoma has not as yet been fully evaluated. Facts now available suggest the potential usefulness of this form of treatment when surgery is contraindicated.

It is obvious that the most complete outline for treatment is of no value unless the proper diagnosis is established. The differential diagnosis is difficult and will always present a challenge because Meibomian tumors are infrequent and they may be confused with conditions which are far commoner. General material in any differential diagnosis may be considered as congenital, inflammatory, neoplastic, traumatic, and degenerative. However, this discussion will be confined to the conditions in the inflammatory and neoplastic catagory that make the differential diagnosis most difficult.

Granulomatous inflammation secondary to syphilis and tuberculosis is as infrequent as chalazia are common, and, though both may be confusing, it is the latter type of lesion that most closely resembles a Meibomian tumor. A chalazion is not a simple retention cyst of the Meibomian gland but a replacement of the gland by granulation tissue containing giant cells of the foreign body type.[42] Variations in this fundamental process may lead to liquefaction in the central portion of the lesion or result in a mass of firm granulation tissue with no definite boundary.[43] The resultant mass in the tarsal portion of the lid with inflammatory signs and a yellowish color may be clinically indistinguishable from a Meibomian tumor. Histologic examination is indicated whenever a lesion clinically resembling a chalazion fails to respond to the customary therapy.

Neoplastic lesions paramount in the differential diagnosis are tumors arising from adjacent sebaceous structures, basal-cell tumors, and tumors metastatic to the lid. Primary lesions from the breast,[44] lung, stomach,[45] and other remote areas may metastasize to the lid. Diagnosis in these cases rests on evaluating the histology of the specimen and considering the over-all condition of the patient. Tumors of the sebaceous glands of Zeis arise in the ciliary line and may present a clinical picture entirely comparable to that of a Meibomian tumor. Histologic examination of a Zeis gland carcinoma reveals an over-all organization and anaplastic cytology identical with that of a Meibomian carcinoma, but the diagnosis is made by the presence of cilia in the lesion and the location of the tumor anterior to the mucocutaneous junction (Fig. 27). In all probability, Meibomian and Zeis

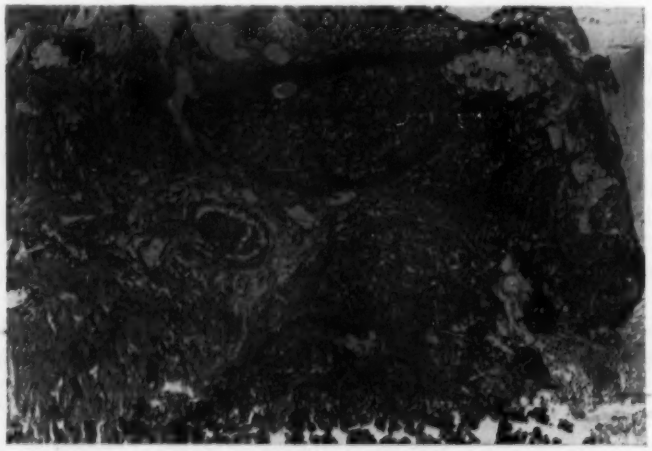

Fig. 27.—Zeis gland carcinoma. Tumor organization and cytology is identical with Meibomian gland carcinoma, but the tumor is anterior to the mucocutaneous junction and a cilium is clearly seen in cross section. Hematoxylin and eosin; reduced from mag. × 110.

gland carcinomas possess equal malignant potential,[46] and so the distinction is of primarily scientific interest.

The final type of tumor to be considered in differential diagnosis is the basal-cell carcinoma. This differentiation is of practical importance because clinical behavior differs and metastasis from a basal-cell carcinoma is exceedingly rare.[47] The basal-cell tumor is most confusing when it arises from the area of the mucocutaneous junction and presents as a mass involving the tarsus and lid margin. Histologic

distinction between basal-cell tumor and Meibomian tumor may be complicated by the presence of one or more isolated cells or small clusters of fully differentiated sebaceous cells within the cell cords of a typical basal-cell carcinoma (Fig. 28). The presence of a few sebaceous cells in an otherwise typical basal-cell carcinoma has never been shown to alter the biologic behavior of the tumor, and these neoplasms are best considered as basal-cell carcinomas.

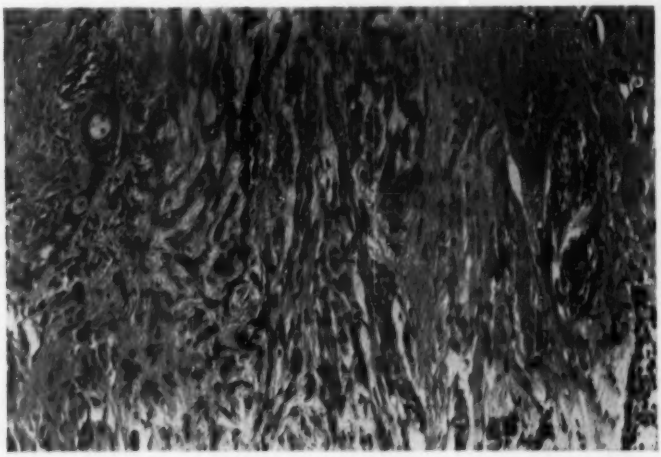

Fig. 28.—Basal-cell carcinoma. Several fully differentiated sebaceous cells are seen in the cell cords of this basal-cell carcinoma. Hematoxylin and eosin; reduced from mag. × 220.

The diagnosis of Meibomian tumor will be made only if the condition is considered in the evaluation of every lesion involving the lid margin or producing a mass in the tarsus. Clinical distinction between a benign and malignant Meibomian tumor is not reliable. Either type should be suspected when prominent local hyperemia accompanies the insidious onset of a lobulated yellowish hard mass.

Addendum

Since this paper was submitted for publication, additional follow-up information has been obtained by the Armed Forces Institute of Pathology. The patient with benign hyperplasia has been followed for three years eight months after surgery, and the three patients with meibomian adenoma have been followed for two years six months, four years three months, and four years five months. No instance of local recurrence or general spread occurred during the observation of these cases.

Summary

Twenty-one tumors of Meibomian gland origin are reported.

These tumors are classified, and histologic criteria for diagnosis are established.

Consideration is given to clinical features of Meibomian tumors, including incidence, appearance, treatment, and differential diagnosis.

Dr. Algernon B. Reese gave advice in the course of this study, and Dr. Arthur P. Stout, of Presbyterian Hospital, and Dr. Lorenz Zimmerman, of the Armed Forces Institute of Pathology, gave assistance.

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Retinal Lesions in Hodgkin's Disease

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Cotton-wool opacities of the retina occur in a number of diseases. They correspond microscpically to agglomerates of cytoid bodies in the nerve fiber layer of the retina.

However, no description of such lesions in Hodgkin's disease has been yet reported in the literature. In a case of uveitis associated with Hodgkin's disease, Kamellin (1944) observed in the macular regions large grayish spots and at the periphery of the retina numerous small white spots "comparable to miliary tubercules." Nothing in the author's description seems to be similar to cotton-wool opacities.

Report of a Case

The patient is a 31-year-old woman without previous significant disease.

In January, 1951, she presented disseminated adenopathies.

In December, 1951, a blood examination disclosed a hypochromic anemia. The patient complained of asthenia, and during the following months she had febrile episodes.

She was admitted to the University medical department (Prof. P. Govaerts) on May 16, 1952, with the major complaints of fever, asthenia, and a moderate degree of icterus. Cervical, axillary, and inguinal lymph nodes were enlarged and hard. The volume of the spleen and liver was increased.

A lymph node biopsy disclosed a typical picture of Hodgkin's disease, with numerous Reed-Paltauf-Sternberg cells. The number of red blood cells was 2,920,000 per cubic milliliter of blood.

X-ray therapy of the cervical and splenic regions was undertaken (from June 2 to 20, 1952), associated with antianemic treatment (blood transfusions, iron, liver). At the end of June the patient was very much improved, afebrile, and stronger. Sedimentation rate was 55 mm/200 in one hour (as against 121 mm/200 in one hour at the time of admission). She had gained 2 kg., but a marked anemia and leucopenia persisted (2,880,000 red cells and 3600 leucocytes per cubic milliliter of blood).

After this remission, she had a relapse in July, with recurrent fever and increased anemia and leucopenia (1,830,000 red cells; 1200 leucocytes).

Icterus developed, with normal liver-function tests and normally colored stools.

The jaundice decreased 15 days later, but on Aug. 19 the patient died, in a state of mental confusion.

Ocular Examinations.—The patient was seen by me for the first time on May 20, four days after her first admission.

Visual acuity was 10/10 for each eye. Full visual fields. The anterior segments were normal.

Small white spots, round or oval, with sharp edges, were disseminated throughout the fundi. They were located along the retinal vessels but did not cover them. Two were present in the right eye, and their size corresponded to one-sixth of the diameter of the disc. One smaller spot was seen in the left eye (Figs. 1 and 2*A*). They had the typical cotton-wool appearance. The discs were normal. There were no vascular abnormality and no hemorrhage.

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From the Department of Ophthalmology (Prof. L. Coppez) and the Department of Pathology (Prof. P. Gerard) of the University of Brussels.

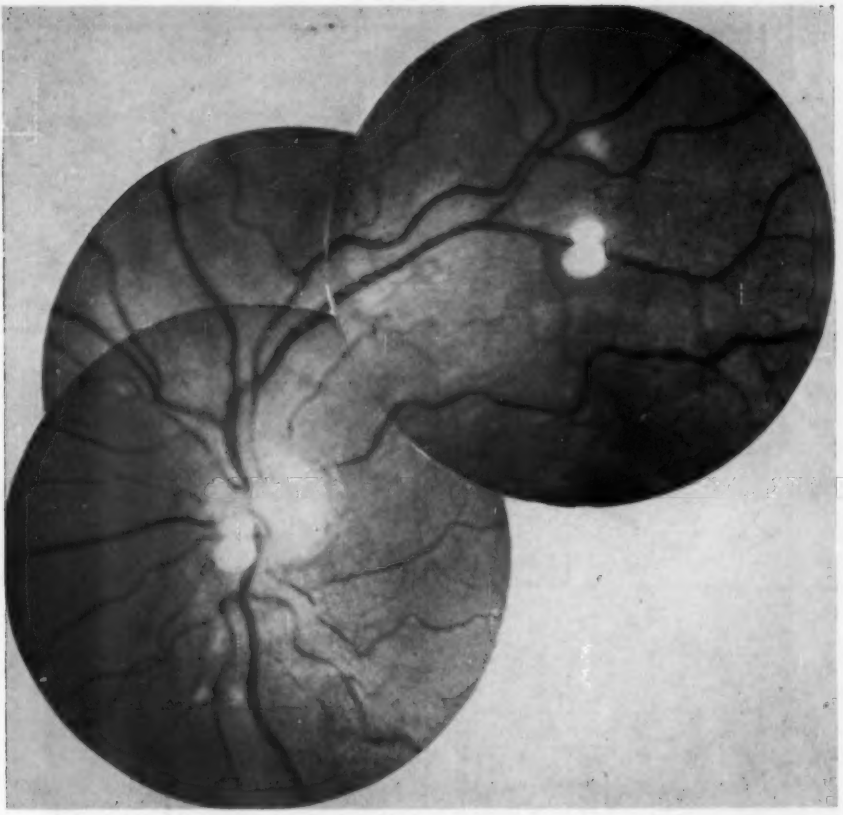

Fig. 1.—Photograph of the left fundus. Note cotton-wool opacities along the retinal vessels.

The evolution of these ocular findings was as follows:

Seven days later, on May 27, three spots appeared in the left eye, similar to those seen on the first examination (Fig. 2*B*). The lesions in the right eye had not changed.

Nine days later, on June 6, during the course of x-ray and antianemic therapy, the lesions in the right eye faded; in the left eye, three of the spots disappeared, while one was becoming paler; two small hemorrhages were present, one isolated, one adjacent to the cotton-wool spot (Fig. 2*C*).

On June 13, the right fundus was normal; on the left only one small white spot remained, with its adjacent hemorrhage (Fig. 2*D*); the veins were moderately dilated.

On June 27 and July 5 and 16, the retinae were entirely normal; the veins were still slightly dilated, and the discs, hyperemic.

On July 26, numerous retinal hemorrhages had appeared along the vessels. No cotton-wool opacity was observed.

On Aug. 6 and 13, numerous new cotton-wool opacities had developed (two in each eye on Aug. 6; a third one in each eye on Aug. 13) (Fig. 2*F* and *G*). The number of retinal hemorrhages had increased. Papillas and visual fields were normal.

A complete postmortem examination could not be obtained, but three hours after death the two eyes were removed and fixed in Zenker's fluid.

Histological Examination.—The normal stratification of the retina was preserved.

In some places, near the retinal vessels, the layer of nerve fibers was markedly thickened by conglomerations of cytoid bodies, globular elements lying between the nerve fibers (Figs. 3 and 4). Some had a uniform aspect; others presented a denser central zone, which stained

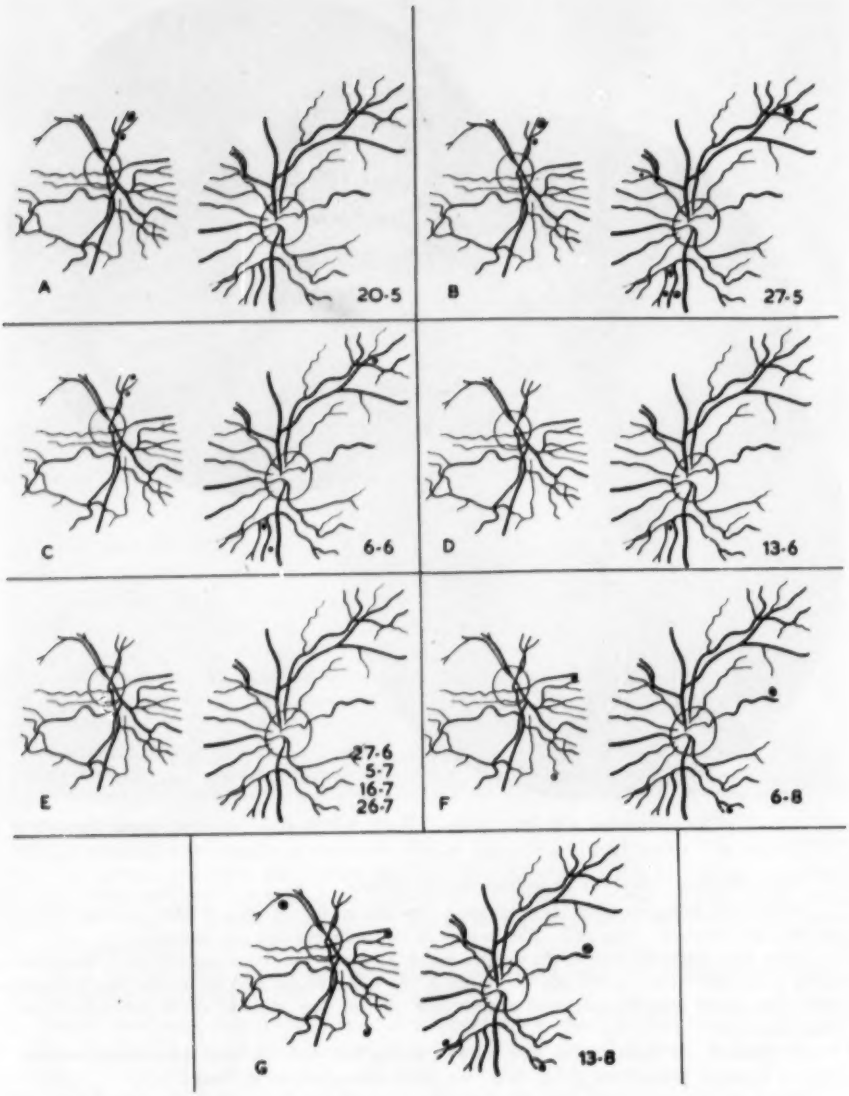

Fig. 2.—Ophthalmoscopic lesions. Diagrams of the evolution of retinal cotton-wool opacities for three months. As soon as x-ray therapy was undertaken, the opacities faded, and they disappeared during one month.

with hematoxylin. The other layers of the retina, choroid, sclera, optic nerve, and vessels were normal.

Thus, in a case of Hodgkin's disease, I had the opportunity to follow for three months the evolution of cotton-wool opacities. The histologic examination proved them to be conglomerates of cytoid bodies.

The lesions were first noticed when the patient entered the hospital, during a febrile episode. During the following days, new spots developed.

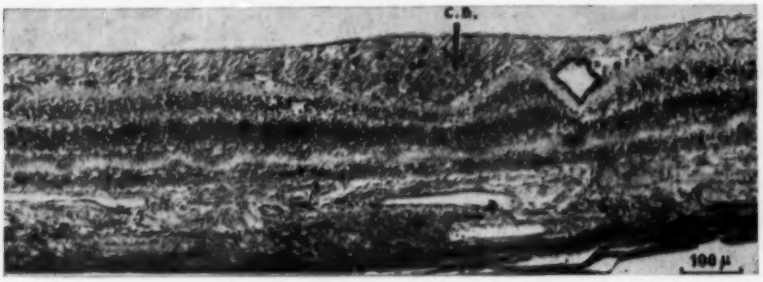

Fig. 3.—Histologic appearance of agglomeration of cytoid bodies, involving the nerve fiber layer of the retina.

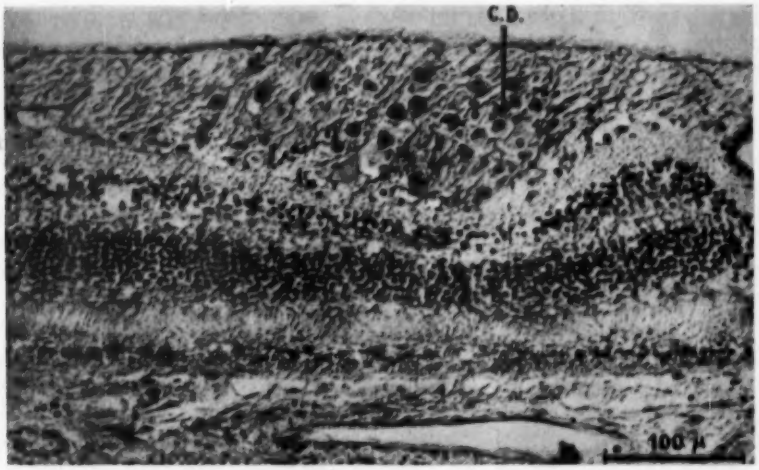

Fig. 4.—High magnification of part of Figure 3. One of the cytoid bodies is clearly visible, with a densely stained central area.

As soon as the cervical and splenic x-ray therapy was begun the retinal lesions progressively faded and no new lesion appeared.

But 18 days after the end of the treatment new white spots had appeared with hemorrhages. The number increased until death.

Comment

The occurrence of white retinal cotton-wool opacities has been described in many diseases: lupus erythematosus, dermatomyositis, periarteritis nodosa (Friedenwald and Rones), scleroderma, leukemia, erythema multiforme, hypertensive retinopathy, Roth's septic retinitis, serum disease (Walsh), retinal tears (Parsons), and also in cases of cachexia (Pick's cachetic retinopathy) and in severe cases of pneumonia (Tumulty, Berthrong, and Harvey) and in severe secondary anemia.

The same lesions have been observed in diseases of the liver and biliary tract: Streiff and Bischler saw them in two cases of cancer of the hepatic ducts ("dysoric retinopathy"); Bonamour, Bonnet, and Buovolo, in one case of cancer of the biliary tract with liver metastases and in no case of cirrhosis with ascites.

None of these patients was anemic or hypertensive. The clinical reports are short and give no information about the state of nutrition or whether cachexia was present.

In 1951 Kiewe and Hart described a case of bronchial carcinoma, in which they saw a white retinal spot, which on histologic examination proved to be a conglomeration of cytoid bodies. The retinal lesion was seen two months before death, and a lymph node biopsy proved the carcinomatous process to be generalized. However, the paper gives no information as to the presence or absence of liver metastases.

In our case of Hodgkin's disease, the patient was anemic and emaciated but not cachectic; the jaundice was of moderate degree. The cause of the jaundice is not clear, as a complete autopsy was not performed.

The anemia or hepatic biliary injury (as in the cases of Streiff and Bischler and of Bonamour, Bonnet, and Bouvolo) could conceivably be considered as responsible for the fundus lesions. But the evolution of these lesions during the three last months of life does not appear to support this interpretation.

During the x-ray therapy, and for a short period thereafter, the general condition of the patient was markedly improved, that is, for six weeks. During this period, no cotton-wool opacity developed, and those already present gradually disappeared (from June 6 until July 26). Thereafter, the patient became worse and the retinal lesions reappeared. Six days before death, as new retinal spots developed, the jaundice was decreasing. On the other hand, the anemia remained stationary during the first two months of stay in the hospital, while the fundus lesions showed modifications.

In conclusion, I may make the following statements: 1. Cotton-wool opacities do not necessarily represent an infiltration by the specific tissue of Hodgkin's disease. 2. No parallelism existed in our patient between the appearance of cotton-wool opacities and the degree of anemia, hepatic injury, or biliary tract disease. The evolution of cotton-wool opacities closely followed the general condition of the patient (as observed in two cases of lupus erythematosus previously described, in 1954).

Until now, I have been unable to determine the factor or factors that brings about the fundus lesions. Ocular examinations of other cases of Hodgkin's disease might throw additional light on the pathogenesis of this curious lesion.

Summary

The clinical observation of a case of Hodgkin's disease with "cotton-wool" opacities in the ocular fundus is reported.

On histological examination, conglomerations of cytoid bodies were seen in the nerve fiber layer of the retina.

The appearance and disappearance of the "cotton-wool" opacities were not paralleled by fluctuations of the degree of anemia or of the hepatic or biliary injury. They correlated closely with the general condition of the patient.

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The Effect of Epinephrine upon the Rabbit Electroretinogram

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Effects of chemical agents upon the eye have long been favored as a means of analyzing the electrical phenomena in response to illumination and of studying the organization of retinal function. In this study the electroretinogram (ERG) serves as a detector of effects which epinephrine (Adrenalin) might exert upon the mammalian retina. Our interest in the substance epinephrine stems from the chemical relationship of epinephrine to the precursor of melanin (as found in the pigment epithelium). Apparently both are manufactured from a basic amino acid, tyrosine. Recent experimental evidence would indicate that the slow waves of the electroretinogram depend upon membrane functions of the pigment epithelium. The electroretinogram therefore would enable us to test whether epinephrine affects specifically the retinal pigment cells.

There are several other facts which point to the possibility of a relationship between epinephrine and pigment epithelium. First, epinephrine readily produces changes in the distribution of the melanin granules in extraocular melanocytes, resulting in the concentration of these granules in the center of the cells. Retinal pigment changes in response to epinephrine occur in lower vertebrates, and they are of the same type as the pigment changes of these species in response to illumination. Second, epinephrine has been reported to affect rather dramatically the frog's electroretinogram, especially by producing a great increase of its slow component (Therman *). After treatment of the light-adapted eye a c-wave of as much as 2 mv. was provoked, when normally it was impossible to record any at all (Granit [4]). A prolongation of the latent period of the electroretinogram and a reduction of b-wave amplitude were associated with this effect.

To our knowledge, a similar electrical effect has never been tested in mammals (where no measurable movement of the retinal pigment granules occurs in response to illumination). It, therefore, appeared worth while to test the effect of epinephrine in pigmented and albino rabbits, with the hope that this might contribute to basic problems of pigment epithelial functions.

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* Reference 5 and Therman,[3] cited by Granit.[4]

Methods

The experiments were performed on 10 female rabbits, both pigmented (2) and nonpigmented (8). After subcutaneous infiltration by 2% procaine and during corneal anesthesia by 5% cocaine, the posterior region of one eye bulb was exposed and the lids were retracted from the cornea. Screw electrodes were inserted into the skull over precentral and posterior brain regions. All animals were tracheotomized and were immobilized for the experiment by tubocurare.

The ink-writing Grass electroencephalograph (Model III) recorded continuously two EEG leads, the electrocardiogram (chest lead), and, on one or two tracings, the potential across the eye. In addition, the A. C.-amplified a- and b-waves were routinely recorded by cathode ray on stimulus triggered sweeps. The simultaneous d-c amplified potential across the eye was either traced by the second beam of this oscillograph or was recorded by two beams of another oscilloscope at different levels of amplification.

The electrodes across the eye were Ag-AgCl wires inserted into glass tubes filled with physiological saline solution. The open end of these glass tubes was sealed by Bentonite paste. The anterior electrode was always placed at the center of the cornea, whereas the posterior electrode made contact with the tissue behind the eye bulb at about the level of the optic nerve.

Freshly prepared epinephrine was injected into a canulated hind leg vein. Only single injections of epinephrine in a total volume of 1 to 2 cc. were administered.

An adaptation period of about one-half hour in the dark was allowed before the start of the experiment. All light stimuli were from Tungsten lamps focused upon the eye. Their intensity was varied by Wratten filters from threshold intensity (ERG) to 20,000 times this intensity. In general, the duration of the light stimulus was either 10 seconds or 1/10 of a second. The interval between two stimuli was at least 2 minutes with the 10-second stimulus duration and 4 seconds (automatically repeating) with the shorter stimulus.

In the following, the term "electroretinogram" is preserved for the electrical changes which result from illumination; "direct-current potential" denotes the potential difference across the eye after dark-adaptation, upon which the electroretinogram is superimposed.

Results

The changes which epinephrine produced were primarily those of the slow waves of the electroretinogram and of the direct-current potential across the eye. In contrast to Therman's findings, the fast components of the electroretinogram, the a- and b-waves at the onset of illumination and the d-wave at the end of the stimulus, remained primarily unaffected, even after the administration of doses which were close to the lethal range. Changes in the slow potential across the eye, however, were elicited with a threshold dose of about 1/1000 mg. in a 2.5 to 3 kg. rabbit. These changes were best and most consistently demonstrated by the c-wave amplitude. They were of two types, which are classified as the "low dose" and the "high dose" effect, and they occurred in both pigmented and albino rabbits, with no apparent difference.

As illustrated in Figure 1, doses of 1/100 and 1/10 mg. of epinephrine produced an increase in the amplitude of the c-wave ("low dose" effect). This reaction was of moderate magnitude. At best it resulted in a threefold

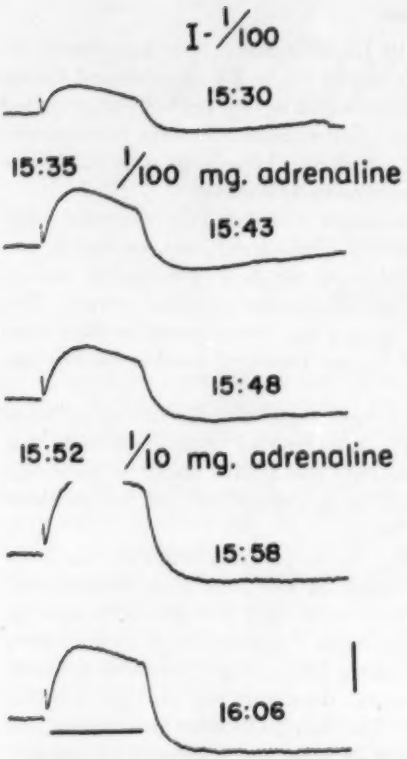

Fig. 1.—Electroretinogram (direct current amplified) after single injections of "low" doses of epinephrine (Adrenalin). Note the increase in c-wave amplitude. The duration of the light stimulus is 10 seconds, as indicated by horizontal line at bottom; its intensity is about 1 lambert measured at the cornea (I = 1/100 of maximal intensity). The amplification is the same throughout; vertical line at bottom denotes 500μ.

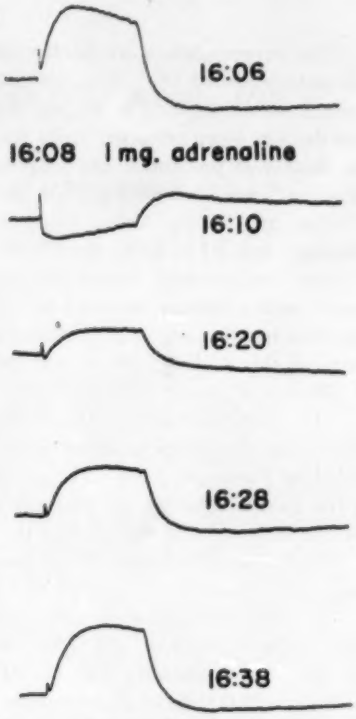

Fig. 2.—Electroretinogram after 1 mg. epinephrine. The Figure continues the experiment of Figure 1, with the same amplification and stimulus duration and intensity. Note that the polarity reversal of the slow wave is not associated with a change in b-wave amplitude. However, during the recovery of the c-wave, the b-wave declines in amplitude.

magnification of the potential if the stimulus intensity was 10 to 1000 times higher than the threshold intensity for the provocation of a c-wave. The effect became manifest within 10 seconds after the injection, and it lasted for more than one-half hour. Its maximum generally was observed around five minutes after the injection.

The second type of reaction in response to epinephrine was provoked when 1 mg. ("high dose") was administered intravenously in one single injection. In response to this dose, the c-wave amplitude rapidly diminished to the extent that the c-wave became replaced by a polarity reversed potential (Fig. 2). The latency of this effect was the same as that of the increase in c-wave amplitude after the administration of lower doses. The reduction progressed for about 100 seconds, at which time the c-wave was replaced by a cornea-negative potential (downward deflection). The electroretinogram maintained this abnormal appearance for three to five minutes. Thereafter

the cornea-negative potential diminished in size; a c-wave-like potential reappeared and progressively increased in amplitude. After 10 to 20 minutes the control appearance of the ERG had been regained.

The change in polarity from the cornea-positive c-wave to a cornea-negative potential was not dependent upon any stimulus parameter. In Figure 2 the duration of the light stimulus was 10 seconds. Since the c-wave normally reaches its peak three seconds after the onset of stimulation, the major portion of the c-wave occurred during illumination. In Figure 3 the

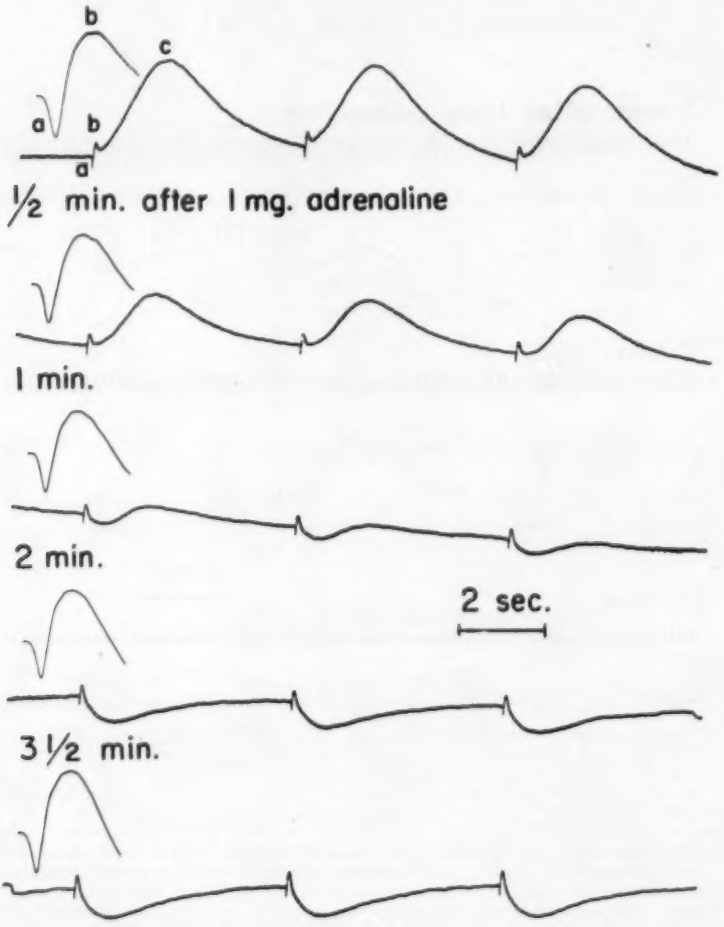

Fig. 3.—Electroretinogram after 1 mg. epinephrine with 1/10 second stimulus. The simultaneously recorded a- and b-waves with increased amplification reveal no change in these waves.

duration of the stimulus was 1/10 of a second; consequently, the c-wave succeeded the stimulus and was curtailed in amplitude and duration compared with the one in Figure 2, despite a 100 times higher intensity of the stimulus. However, the effect of 1 mg. of epinephrine was the same in the

two experiments, i.e., the c-wave was replaced by a cornea-negative swing. The high dose of epinephrine provoked severe effects upon the heart

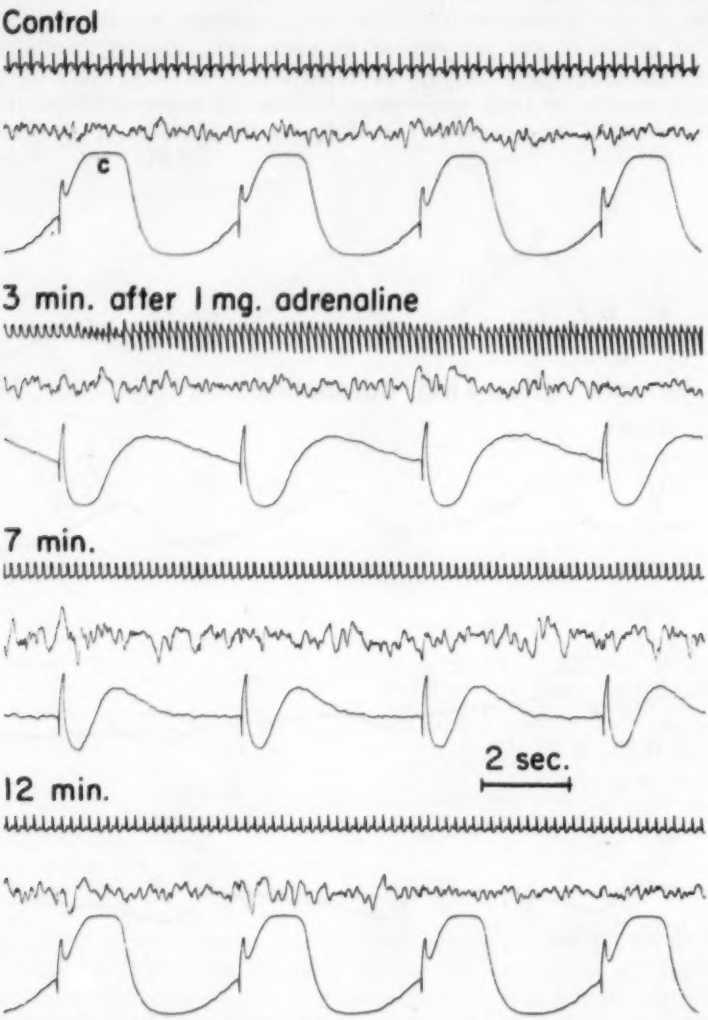

Fig. 4.—Effect of 1 mg. epinephrine on electrocardiogram (upper line), electroencephalogram, and frontoparietal (middle line) electrogram and electroretinogram (lower line) recorded by electroencephalograph. The slow waves of the ERG are distorted because of A.C. amplification. The reversal in polarity of the slow wave is, however, clearly evident. Note the marked effect on the electrocardiogram and the rapid recovery of the ERG.

(Fig. 4). Marked constriction of the blood vessels of choroidea and iris were clearly evident. The question, therefore, arose as to whether the change in the electroretinogram resulted from inadequate blood supply to the eye and its various consequences. Three different procedures were used to test this possibility: production of ischemia of the eye by increased intraocular pressure through a needle in the anterior chamber connected to a saline solution

under 80 to 120 mm. Hg pressure; production of "cardiac arrest" following intravenous injection of air; production of hypoxia or anoxia by exposure to low oxygen concentrations. The results obtained with these procedures confirmed earlier observations [6] that ischemia, asphyxia, or anoxia produces (in rabbits) the disappearance of the c-wave without replacement by a cornea-negative swing. The c-wave disappearance was, moreover, associated with a simultaneous reduction of a- and b-waves, which was not observed

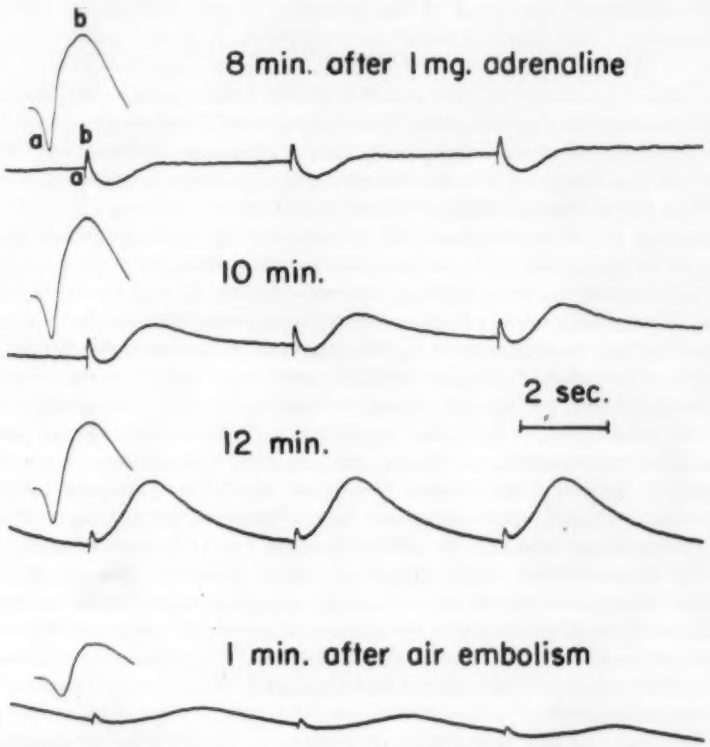

Fig. 5.—Recovery from the effect of 1 mg. epinephrine and subsequent effect of lethal air embolism on electroretinogram. The eye is stimulated by repetitive flashes of 1/10 second duration and of high intensity (100 lamberts). The interval between flashes is four seconds. The D.C. amplified electroretinogram is continuously recorded while single cathode ray sweeps trace the a- and b-waves on faster baseline and with higher magnification. The illustrated a- and b-waves belong to the first response of each line. The animal was killed by air embolism 13 minutes after the injection of epinephrine. The control tracings of this experiment were similar to those recorded 12 minutes after epinephrine.

with the effect of epinephrine. Figure 5 serves to illustrate this point in a rabbit which was killed by air embolism after the epinephrine effects had been tested. One notes that a small c-wave is still present when a- and b-waves have become reduced in amplitude as a consequence of the interrupted blood supply to the eye.

After a high dose of epinephrine, the a- and b-waves remained unaffected while the c-wave disappeared. However, the restoration of the c-wave 10 to 30 minutes after the injection was often associated with a fall in b-wave

amplitude (see Fig. 2). Choroidal circulation was still reduced at this time, and it is possible that the delayed decline of the b-wave reflected impaired retinal nutrition.

The direct-current potential across the eye changed in response to epinephrine in the same manner as the c-wave. With "low" doses of epinephrine the direct-current potential rose by ½ to 2 mv.; reversely, the direct-current potential usually decreased when a "high" dose of epinephrine was administered. In general, however, the changes in the direct-current potential were less consistent than those of the c-wave.

Comment

The slow waves of the electroretinogram, which reflect the effects of epinephrine upon the retina, have been largely neglected in the past, owing to uncertainties of their origin and their functional significance. Recent studies [1] on the origin of the electroretinogram provide, however, a working hypothesis for the interpretation of changes in these potentials.

According to this hypothesis, the slow potentials develop across the pigment epithelium as the result of ion-concentration differences and ion movements, in response to illumination, between the retina and the outer ocular sheaths. Two components of this potential were established; the one resulting from "active" ion-transport by the pigment epithelium, the other originating from a "passive" physicochemical membrane effect of the structures which surround the retina and impose a barrier to the free movements of ions. The slow waves which one normally records across the eye are the sum of these two membrane effects. Hence, after elimination of the active ion-transport function only those potentials appear in response to illumination which depend upon the presence of "passive" membranes. For example, intravenous injection of sodium iodate, by its selective action upon the pigment epithelium, eliminates the c-wave within a few minutes and results in the replacement of the c-wave by a cornea-negative potential. The explanation is that the c-wave represents a potential generated by active ion-transport whereas the cornea-negative potential reflects the appearance of ionic differences between retina and choroidal blood across "passive" and inactive membranes.†

On the basis of this hypothesis, the effect of a high dose of epinephrine is interpreted as evidence of a direct and massive action of epinephrine upon the pigment epithelium which temporarily almost abolishes active ion-transport. Our experiments do not reveal by what mechanism epinephrine produces this effect, but one is inclined to assume that only a profound change can achieve such a drastic result.

The qualitatively different effect of a low dose of epinephrine is interpreted as a "stimulating" action of this hormone upon the specific membrane functions of the pigment epithelium. It is conceivable that this action may be mediated by the humoral changes which epinephrine produces by its actions elsewhere in the body, e.g., in the liver. However, the fact that

† The active ion-transport function of the pigment epithelium apparently serves the cancellation of ionic differences between retina and chorioidea in response to illumination. In its attempt to reestablish ionic equilibrium, the pigment epithelium, however, tends to overshoot and to produce a potential which is greater than necessary to cancel the cornea-negative potential of the passive membrane effect. The c-wave is the result of this overshoot.

Therman ‡ produced a similar change by direct retinal application of epinephrine in the isolated frog's bulb suggests that the low-dose effect of epinephrine is also a direct one upon the pigment epithelium. Moreover, it has been shown, although also in the frog, that epinephrine enhances active ion-transport through the isolated skin epithelium (Ussing [7]). This may serve as a general indication that epinephrine is at least capable of affecting membrane properties.

Our experiments do not permit more than a cursory discussion of the significance of the epinephrine effect upon the pigment epithelium. Epinephrine may have normally a regulating function upon the membranes of the epithelium, but the magnitude of its effect in the rabbit is so small with physiological doses that we doubt that this influence is of any great importance in mammals. With respect to the general physiology of the pigment cell, our findings allow the following tentative conclusions:

1. The interpretation of the epinephrine effect on the ERG as evidence of changes in the pigment epithelial function implies that the membranes of the pigment epithelium contain an epinephrine-sensitive component. This may be independent from the presence of melanin granules, since albino rabbits show the same changes as pigmented animals. The reactiveness of this membrane component may, however, be related to the ability of the pigment epithelium to react with changes in pigment distribution. The increase of the c-wave measured in the rabbit is small compared with that recorded by Therman in the frog, where, in contrast to mammals, the pigment granules are able to migrate toward the visual cells.

2. The epinephrine effect upon the pigment epithelial membranes is in low doses similar to that of illumination: Epinephrine augments the c-wave; illumination provokes the c-wave, and the c-wave amplitude is the higher the greater the intensity of illumination. Since the pigment movements in lower vertebrates in response to epinephrine are also the same as those provoked by illumination, it is suggested that membrane change and pigment migration are intimately linked and that the membrane change may be responsible for the pigment movements. Illumination most likely causes these changes by a disturbance of the ionic equilibrium in the outer layers of the retina, whereas epinephrine probably produces these changes by a direct membrane effect.

3. The effectiveness of a high dose of epinephrine in apparently blocking active ion-transport suggests that the pigment cell is metabolically more sensitive to epinephrine than other cells. It therefore appears that metabolism and membrane function of pigment cells should be considered as possible sites of actions for all effects which seemingly involve only the melanin apparatus.

Summary

The effectiveness of epinephrine (Adrenalin) in doses ranging from 1/1000 to 1 mg. administered intravenously was tested by the electroretinogram (ERG) in unanesthetized albino and pigmented rabbits during immobilization by curare. The most reactive component of the ERG was the c-wave; a- and b-waves remained essentially unaffected, whereas, the d-c

‡ Therman,[8] cited by Granit.[4]

potential across the eye changed in the same direction as the c-wave. There was no difference between albino and pigmented animals.

"Low" doses of epinephrine of 1/1000 to 1/10 mg. produced a moderate increase in the amplitude of the c-wave which began approximately within 10 seconds after the injection and lasted for at least one-half hour. "High" doses (1 mg.) rapidly diminished the c-wave and resulted in the temporary replacement of the c-wave by a cornea-negative potential similar to the effect of sodium iodate. This effect differed significantly from that produced by ischemia or anoxia.

The augmentation of the c-wave corresponds to the findings of Therman with the isolated frog eye; the change in the rabbit is, however, of relatively small magnitude. The effect of epinephrine is briefly discussed and related to membrane changes of the pigment epithelium.

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Tonometry and the Cornea

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The cornea receives a slight amount of trauma from tonometry. This is more readily observed when fluorescein is used in the eye and examination is made with the aid of a slit lamp. At first, the subject appears to be one of rather academic interest, as there seems to be no excuse for inflicting injury on the cornea with the tonometer. However, in recent years, with the increasing use of tonometry, the advent of tonography, and now phasic tonography,[64] there is a more serious threat to the corneal epithelium.

Though some authors * have mentioned the possible danger of tonometry, there is apparently no existing description or illustration of what happens to the cornea during this procedure.

An attempt has been made in this study to find ways and means of lessening the dangers inherent in tonometry as popularly practiced. Factors such as the following have been considered: local anesthesia; the precorneal fluid; the technique of tonometry with special reference to physical trauma as determined by motion, weight load, and time values; and possible alteration of the instrument itself.

The material assembled here has been gleaned from the examinations of more than four thousand eyes subjected to indentation tonometry under many different conditions. Since little has been written on the immediate subject, pertinent literature of relatively recent date is reviewed, and results of experiments are reported. Following this, the matter is discussed with relation to such questions as the reasons for injury to the cornea during tonometry, the appearance and the clinical significance of the injury inflicted, and how such injury may be avoided.

Literature Review

In all the literature on tonometry a constant striving for greater accuracy is evident, but little is said of the case for less injury to the cornea. Priestly Smith[1] omitted all reference to the matter. Freiman[19] made a clinical study and review of tonometry in which he noted that McLean and Duke-Elder each stated that capillary attraction may impair the accuracy of the Schiøtz instrument. He maintained that intraocular tension dropped during general anesthesia, and was highest under local anesthesia. (This matter is now under investigation by the committee on standardization of tonometers.) Schiøtz on the other hand, felt that the factor of capillary attraction was negligible. As far back as 1927 he realized that the deflections given by different tonometers were not comparable if the plungers were differently shaped. While Schiøtz convinced himself that his tonometer X had nothing of sufficient value to warrant its adoption, he seems not to have considered the matter of corneal injury.

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* References 2, 6, and 52.

Duke-Elder † stated that the Schiøtz tonometer X with convex plunger base was more useful than the standard model because it could deal more accurately with a wide range of tensions. This model involved less risk of trauma to the cornea, a statement later made also by Friedenwald [6] and by Sugar.[52]

Posner [17] pointed out that there is under any circumstances a certain amount of friction between the plunger and the cylinder through which it moves.

Friedenwald [44] described how the footplate of the tonometer flattened the cornea and how the plunger indented this flattened area.

Jackson [61] thought it unlikely that the Schiøtz type instrument would be replaced.

The decennial report for 1954 [65] of the committee on standardization of tonometers, compiled by several authors, is a treasure house of information. A few excerpts from this report are applicable: Where readings differed by one half of one scale unit or more, the position of the eye may have been different, or there may have been more or less friction between plunger and barrel. It has become clear that the weight of the plunger assembly, the diameter of the plunger base, and the plunger edge profile are the essential factors in tonometry. Indentations by plungers with flat or concave bases have the same shape, since the edge and not the center of the plunger base impinges on the cornea. The radius of curvature of the edge of the plunger is thought to be the most critical of all measurements; the sharper the plunger edge the lower is the scale reading.

Friedenwald and Buschke [24] reported that trauma inhibited mitosis in the injured area of the corneal epithelium for several hours. Healing during this period occurred by cell migration. The same authors observed [25] a strong inhibition of the mitotic rate in the corneal epithelium following injury. Epithelial movement in the rat cornea after superficial injury was slowed down by topical application of cocaine or pontocaine.

It was found by Gundersen and Liebman [21] that 0.5 percent tetracaine hydrochloride was one of the least toxic of the local anesthetics as measured by the inhibition of corneal regeneration.

Leopold [28] asserted that detergents, for example Zephiran 0.1 percent, produced corneal damage, as evidenced by minute staining areas, and also retarded regeneration. He ventured the opinion that they probably act by denaturing proteins.

Buschke, Friedenwald, and Moses [30] reported that nuclear fragmentation occurred in the upper layers of the corneal epithelium following ultraviolet irradiation. This effect was closely correlated with clinically visible roughening and stippling of the corneal surface in photo-ophthalmia. Fragmentation occurred only after a lag period and apparently required oxidative processes.

Buschke, Friedenwald, and Fleischmann [20] observed that cocaine inhibited the rate of healing and the mitotic activity following superficial injury to the corneal epithelium. Even a short ether anesthesia markedly inhibited entrance into mitosis.

Buschke [34] warned that, among other substances, mercurials inhibited

† References 4 and 7.

cell movement and caused loosening of epithelium from stroma after incubation.

Friedenwald and Heerema [48] reported that lanolin retarded wound healing more than petrolatum. However, washed lanolin did not so retard healing.

Marr, Wood, and Storck [53] stated that butyn sulphate, tetracaine hydrochloride, pilocarpine, and fluorescein all prevented regeneration of the corneal epithelium in enucleated eyes in contact with these drugs in buffered solution for three hours.

Duke-Elder again noted [67] that vital activity was inhibited by local anesthetics.

We were reminded by Theodore [58] that drugs put in the eye may be primary irritants, or sensitizers, or both. He warned against use of metaphen, merthiolate, and other mercurials as preservatives in ophthalmic preparations. Many other drugs, even ophthalmic cortisone, could produce allergy in the eye.

It was shown by Friedenwald, Buschke, and Crowell [29] that after injury to corneal epithelium by a sharp instrument a phospholipoid substance was exuded into the wound. This did not happen in injuries inflicted by blunt instruments.

Verhoeff,[33] discussing a paper by Friedenwald, admitted that the Souter tonometer caused disturbance in corneal epithelium such that vision should be determined before tonometry.

Kronfeld [55] observed that a slight foreign body sensation of about three hours duration followed tonography. He had seen no complication attributable to the procedure.

Horwich and Breinin [64] reported that 50 percent of cases undergoing phasic tonography showed undesirable abrasions, and he suggested that such tests be performed at variable times on different days to avoid such injury.

Duane,[41] discussing the steady state of corneal hydration, stated: "We have not investigated how much trauma is required to change transparency." It was his opinion that opacities occurred because of an inhibition of the protective action of the semipermeable membranes. He also wrote an excellent review of work on metabolism of the cornea, giving valuable references.[40]

Cogan [15] found that full-strength glycerine used either as drops or as tablets made from infant suppositories substantially cleared corneas hazy from edema in from fifteen to thirty seconds. Under the slit lamp, clearing could be seen taking place beneath the glycerine layer. No anesthetic was used.

Swan [57] described use of 2 percent carboxymethylcellulose in glycerine to help clear corneas hazy from edema. Clearing occurred in two to three minutes and lasted longer than when glycerine alone was used. The preparation is quite viscid and can be placed on the cornea and spread with a glass rod. He also reported [27] use of methyl cellulose in ophthalmology. Tetracaine was said to be absorbed and its action retarded by methyl cellulose, which, however, has cohesive, emollient, and lubricating qualities.

Friedenwald, Hughes, and Hermann [31] observed that when the cornea was irrigated with one-tenth normal hydrochloric acid a "lacy network of fine punctate opacities appeared in the exposed area of the cornea, gradually

coalescing into a smooth, dense opacification." That part of the cornea loosely covered by the lids was sharply demarcated.

Cogan [43] explained that in sleep, when there is no evaporation of tears, edema occurs because osmotic tension becomes greater in the epithelium than in the tears. The same author stated [51] that clouding of the cornea due to stretching resulted from water being squeezed from an intra- to an extramicellar situation. He found [9] in experimental animals that when the cornea was partially protected by the nictitating membrane, vesiculation occurred more intensely in the exposed portion when water was used for irrigation, and in the protected area when hypertonic saline was used. Moisture seemed essential to the vesiculation process. Bullae were quite common in glaucoma, where Fischer (quoted by Cogan) reported an increase in the salt content of the cornea. According to Cogan,‡ edema produced by cocaine is due not to toxicity of the drug, but to hypotonicity of the solution used. There was less drying with 10 percent than with 4 percent solutions. The edema was not produced if the lids were kept closed. Clouding of the cornea was prevented in surgical procedures, in glaucoma, and in the case of contact glasses if a 1.5 percent salt solution was used.

Simpson,[38] writing on corneal edema, stated that it was recognized as vacuolation seen best by retroillumination. It stained diffusely, was rough, dull, hazy, and reversible.

Berliner [16] recorded that the state of the epithelium seems to be a sensitive index of corneal health. Edema of the cornea may be evanescent or permanent. Its presence rarely predisposes to erosions, ulcers, and deeper changes. Minute epithelial changes may be due to intracellular inclusions, to intercellular coagula, or may follow the collapse of vacuoles.

In discussing wetting agents, Bellows and Gutman [18] said that aerosol in 5 percent solution caused haziness of the cornea. This cleared by the following day.

Kronning [42] showed that pseudokeratoconjunctivitis sicca reactions could be obtained by repeated instillations of local anesthetics. Drying of the epithelium, toxic effect of the agent, and osmotic pressure could all effect the disturbance. Preservatives did not cause these results. The drying effect of air was found to have less significance than was formerly believed.

Smelser [54] believed that the optical properties of the cornea were due not only to osmotic pressures but also to atmospheric oxygen metabolism. He prevented development of halos in contact lens wearers by keeping an oxygen bubble between cornea and glass. Halos appeared rapidly if the hydrogen ion concentration was lowered.

Smelser and Ozanics [56] reported that corneal haze occurred in two hours when contact lenses were used on guinea pigs. Corneas became thickened from edema. They observed a striking depletion of the glycogen content of the corneal epithelium, but made no mention of physical epithelial changes as a factor in corneal haze.

In a personal communication, Smelser [76] doubts that hydration (edema) of the corneal epithelium occurs during the short time the tonometer is applied. It may be, he stated, that the turbidity observed in this case is due to tension placed on the corneal fibers. This is known to produce a

‡ References 10 and 11.

change in the refractive index of corneal structures.

Hosford and Hicks [5] believed that sensations of the patient were more closely related to hydrogen ion concentration than to osmotic pressure. This is important when drops have to be used frequently or over long periods of time.

The excised bovine cornea was said by DeRoetth [46] to have a steady rate of respiration regardless of the hydrogen ion concentration of the suspending medium.

Schaeffer [47] found that 0.9 percent sodium chloride was to him the least irritating fluid for instillation into the eye. Within limits of tolerance, changes in osmotic tension did not seem to induce physical changes in the corneal epithelium.

Potts [59] found that tears correspond to 1.35 percent salt solution as judged by observer response. Working with radioactively labeled salts, he found that the corneal film has a higher osmotic optimum than is generally reported, and he raised some doubt as to the explanation of corneal deturgescence on any theoretical basis.

Cogan and Hirsch [23] found that salts did not penetrate the cornea, and, like other authors, they maintained that the tears are good buffers and determine the hydrogen ion concentration of weak solutions as soon as they are put into the eye.

Holt and Cogan [32] showed that corneal epithelium offered great resistance to passage of ions.

According to Morrison,[63] penetration of drugs may be very rapid following local anesthesia and tonometry. Hydrogen ion concentration and buffering are important only as regards stability of solutions, as tears are excellent buffers. He quoted Ginsberg and Robeson to the effect that detergents increase penetration of drugs, possibly by "solubilizing" the intercellular cement substance of corneal epithelium.

According to Swan and White,[13] disturbance of the surface epithelium increased its permeability to all drugs. Where the epithelium was intact, water-soluble drugs in oil and fat-soluble drugs in aqueous solution penetrated more readily. Pontocaine had a high surface activity and penetrated well when the epithelium was intact. All drugs seemed to penetrate equally if the stroma was exposed. Changes in intraocular pressure did not affect absorption of drugs.

Welsh [60] stated that methyl cellulose did not support bacterial growth, 0.5 to 0.8 percent being optimal for eye use.

Terry [8] observed that the cornea may derive some nutrition from tears as well as from limbal vessels and aqueous.

Cogan and Kinsey [14] admitted that it is hard to prove that the fluids on the cornea are hypertonic, but osmotic pressure of the tears is certainly increased by evaporation. The normal state of hydration represents an equilibrium between the inherent imbibitory capacity of the corneal stroma and osmotic forces acting at the corneal surfaces. Loss of corneal fluid by osmosis provides a means of circulating oxygen through the stroma from the blood via the limbus.

According to Swan,[39] the precorneal film never became so viscous that bubbles were retained, because evaporation stimulated tearing. There is

considerable disagreement about the physical and chemical properties of tears. He found no anesthetic that did not impair epithelial growth. Changes in the epithelium were largely eliminated if hypertonic or isotonic solutions of the anesthetic were used. He believed that some alteration in the physicochemical state of cells occurred from topical anesthesia. He liked methyl cellulose as a vehicle, but not oils which tended to produce mechanical irritation despite lubrication. Local anesthesia and massage with a glass rod were used to reduce bedewing in glaucoma. Wetting agents improved contact and directly influenced permeability of the epithelium. He thought that anesthetics acted more rapidly in alkaline solution.

Courtney [62] discussed the physiology of the precorneal film which consists of three layers. The deepest layer contains aminopolysaccharides from the conjunctival globlet cells, and must be kept in contact with the epithelium (Vidal quoted by Courtney). The middle layer is fluid and contains mucolytic and proteinaceous material from the lacrimal glands. It maintains moisture. Hyaluronidase in these two layers assures low surface tension. The outer layer is lipid and is formed from secretion of the meibomian glands. It serves as a wall in front of the tear fluid and prevents too-rapid evaporation. The amount of tears is not as important as their quality. The corneal welfare is threatened by trauma, inflammation, or degenerative changes in the nonlacrimal glands. Detergents adversely affect the vital oil film.

No evidence was produced by Hermann and Hickman [36] in favor of the presence in corneal epithelium of an intercellular cement. Cohesion decreased when corneas were bathed in weak, higher aliphatic alcohols, and loss of cohesion was not a consequence of inflammation nor a manifestation of death of epithelial cells.

Friedenwald stated [40] that there are some similarities but also some major differences between forces that bind epithelial cells to one another and forces that bind the epithelial sheet to underlying stroma. Anionic detergents abolished intercellular cohesion, but cationic and nonionic detergents were without effect. Some local anesthetics followed by incubation caused a loss of cohesion. Pontocaine [12] and chlorobutanol inhibited respiration and glycolysis in the cornea. This effect was additive.

Some organization of corneal epithelium is lost following injury, according to Buschke, who recorded [45] that loss of cohesion between epithelial cells occurred when cocaine or pontocaine was injected into the stroma. Some detergents directly caused cohesion loss, in short periods dissociating epithelial sheets into individual cells.

Jakus [66] found that each cell of the corneal epithelium was a separate unit having no direct connection with others. In a personal communication,[74] she stated that the squamous cells can be separated from one another much more easily than can wing cells or basal cells. She assumes that this is the result of squamous cells having much smaller peripheral processes, " much more feeble zipper"! She goes on to say that only the greatest care in handling keeps these outer layers in place; even then individual squamous cells or layers of several of these cells will often be separated by some micra. She therefore tends toward the belief that, in the living cornea, applied pressure (as from a tonometer) could force

some of these cells apart or slide a layer of them over the adjacent layer and thus open up temporary channels into which fluid might flow. She has observed that the cells themselves are fairly tough and do not often show tears in their membranes; thus, if they were able to reestablish contact with each other, they could (quickly) repair damage caused by the tonometer.

Materials and Methods

Recorded examinations of more than four thousand corneas on which indentation tonometry was done are the chief sources of information in this study.

Records were kept as to age, sex, race, state of health, pathology in the eye, refraction, tension (Schiøtz), weight of plunger load, time of application of the tonometer, and injury to the cornea as evidenced by diffusion of fluorescein seen under slit lamp examination.

Tetracaine hydrochloride (pontocaine), 0.5 percent, was routinely used for anesthesia, two drops being placed in each eye at intervals of approximately one-half minute. It was found possible to measure intraocular pressure in a few cases, including my own, without anesthesia.

In all calculations, eyes known to be glaucomatous and those with manifest external disease were omitted. The only exception to this was the study of cases submitting to tonometry without anesthesia. Here all cases with pressures of 25 (Schiøtz) or less were included.

In recording the amount of diffusion of fluorescein into the cornea, or so called "staining," the figures zero to four were employed. This method of grading has been found practically reliable by Friedenwald [22] and others. A one-plus or minimal stain was one barely perceptible or difficult to see even under the slit lamp. A two-plus stain was easily seen, but it involved no more than one-fourth of the area of the cornea exposed to pressure by the tonometer. A three-plus stain involved one-quarter to one-half of the area so exposed. A four-plus stain involved more than one-half of the corneal surface presumably in contact with the plunger and the footplate. It is possible or even probable that different observers would get slightly different quantitative results using this method. However, findings should be relatively the same, even though it is admittedly difficult to differentiate the amount of disturbance due to pressure of the tonometer, the anesthetic itself, or exposure resulting from the anesthetic.

Fluorescein, 0.5 percent, in normal saline gave excellent results. A glass rod was used to apply it, and irrigation was not done, since diffusion areas could be seen well and the precorneal film could more readily be studied without it. Fluorescein 0.5 percent is not irritating and does not itself produce lesions on the human cornea, although Friedenwald has reported that fluorescein causes fine punctate stippling in the rabbit's corneal epithelium.[48]

In all tonometric tests the patient was in a semireclining position with gaze fixed directly above at a ceiling target. In all cases where comparisons were attempted, every effort was made to secure the same size drop delivered by the same technique to each eye. A stop watch was used in observations having to do with time values. Standard Schiøtz tonometers were routinely used. Later the plunger edge of one of these instruments

was rounded, and later still a small segment was removed from the plunger base and footplate.

Glass and metal blunt rods with radius of curvature about 2 mm. and a smooth metal edge with a radius of curvature about one-eighth of 1 mm. were used to see the effect of blunt and relatively sharp massage and pressure on the cornea.

In looking for some substance which might be used to protect the cornea from the tonometer, the silicones were considered. These have found some application in other fields of medicine. The Dow Corning Corporation furnished several "Corning 200" fluids of various viscosities with which to experiment.

Methyl cellulose, 4,000 centipoise, 1 and 2 percent, was supplied by Alcon Laboratories. This was effectively used under circumstances to be described.

To note the effect of capillary attraction, experiments were carried out on a small rubber balloon, made from a surgical glove, about the size of the eye and inflated to approximately normal intraocular pressure. The tension in this balloon was checked before and after experiments to see that it remained constant. Methyl cellulose in various strengths was dropped on the balloon, and the tonometer, bearing various loads, was then placed upon it as though measuring the intraocular tension. Records were kept of the scale readings.

Results

In general it was noted that in young and healthy individuals there is noticeably less trauma done to the corneal epithelium by the tonometer. The younger the individual, the less the staining.

TABLE 1.—*Minimal or No Staining After Tonometry*

Age	Number of Cases	Per Cent
25 years or under	88	68
26 to 50 years	200	43
51 to 69 years	250	38
70 years or over	106	36

No relation was established between staining and sex or race.

No relation was observed between refractive errors and staining after tonometry. The following groups were compared; plus equivalents of two diopters or less (274 eyes); plus equivalents of four diopters or more (16 eyes); minus equivalents of two diopters or less (71 eyes); minus equivalents of four diopters or more (15 eyes); cylindrical errors of less than two diopters (210 eyes); and cylindrical errors of two diopters or more (18 eyes). Though the number is small, staining in each group was so nearly alike as to discourage further investigation. Aphakic eyes have no peculiar staining characteristics.

Records were kept for some time of the amount of blinking, rolling, and squeezing of the lids. Forty-six eyes, including 4 with nystagmus, were recorded as exhibiting these features in the order of four plus. These were compared with 46, chosen at random during the same period of observation, which showed none of these features.

TABLE 2.—*Motion: Average Staining in Ninty-Two Eyes*

Time	Motion Four Plus (46 Eyes)	Motion Zero (46 Eyes)
Momentary	1.4	1.6

The figures show that there was no more corneal disturbance where there was blinking, squeezing, rolling of the eyes, and nystagmus. This is not as illogical as it seems. Where there is decided or more or less continuous movement, the weight does not rest so continuously on any one area and, when squeezing and blinking occur, any increase of pressure from the lids is transmitted to the larger area under the footplate and not to the area beneath the plunger. Furthermore, when one realizes he is dealing with a highly emotional or nervous person, he naturally takes added precautions to perform his task with minimum trauma and utmost speed. It is only fair to state that scale readings in these cases may be far from accurate.

Similar reasoning applies to the study of 17 eyes on which it was possible to take tensions without anesthesia. Two of these were my own.

I was not able to correlate pathology within the eye to the amount of trauma done the epithelium of the cornea by tonometry. The one exception

TABLE 3.—*Anesthesia: Average Staining in 217 Eyes*

Time	With Anesthesia (200 Eyes)	Without Anesthesia (17 Eyes)
Momentary	1.7	0.6

was glaucoma, in which the eye stains badly when the tension is above normal.

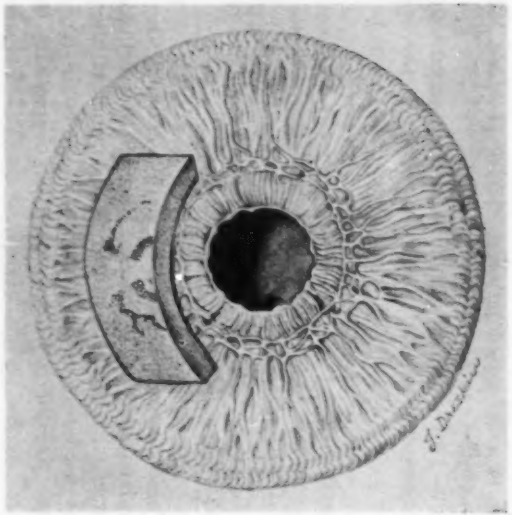
The first eye tested almost always showed the greater disturbance after tonometry. This was not so if the tonometer was carefully wiped and dried between tests on the first and second eye. On inspection of the base of the footplate and plunger, after the tonometer had been used on the first eye, scattered droplets of tears could be seen. These provided lubrication and protection for the epithelium of the second eye.

When a drop of 1 percent methyl cellulose was placed upon the cornea just before the tonometer was applied, disturbance of the epithelium was greatly reduced.

TABLE 4.—*Methyl Cellulose: Average Staining in 300 Eyes*

Time	No Methyl Cellulose (100 Eyes)	1% Methyl Cellulose After Anesthesia (100 Eyes)	0.5% Pontocaine in Methyl Cellulose 1 % (100 Eyes)
Momentary	1.7	0.5	2.6

When pontocaine was incorporated in methyl cellulose, toxicity was increased. The explanation lies in the fact that methyl cellulose keeps the anesthetic in contact with the cornea for a longer time. If, therefore, methyl cellulose is to be used for corneal protection, it should be instilled after the eye has been anesthetized and tears have removed the excess of anesthetic.



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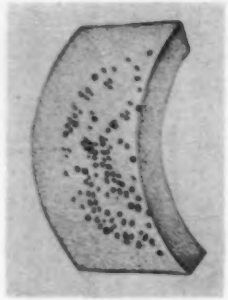

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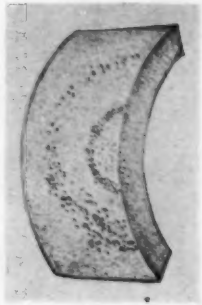
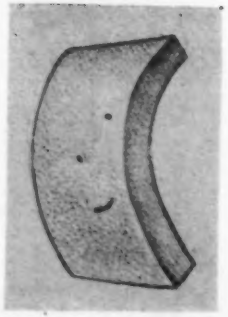


C

D

Fig. 1.—Characteristic disturbances of the cornea following tonometry. *A*, pressure bruises cornea. No bruise occurs where wedges have been removed from tonometer. *B*, sensitivity to pontocaine (or other topical anesthetic). The spots are large, rounded, and often confluent. *C*, pressure effect. Stippling more concentrated in plunger edge area. *D*, effect of exposure and drying. *E*, example of one-plus staining. *F*, example of two-plus staining. *G*, example of three-plus staining. *H*, example of four-plus staining. *I*, "chicken wire" effect occasionally seen in plunger area. *J*, combined pressure and drying effects. *K*, sunflower effect. *L*, radiating effect from pressure of instrument, due to changes in refractive index.



E

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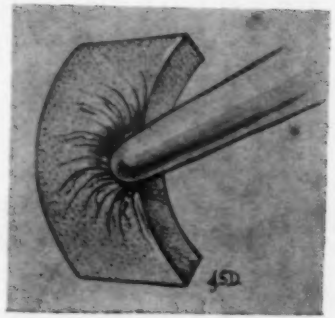

L

In the course of this study it soon became apparent that the amount of epithelial disturbance varied directly with the weight of the plunger assembly. In observations on the relation of weight and time to injury, staining in the plunger area only was used.

Nearly all cases in which tonography was employed showed four-plus

TABLE 5.—*Weight: Average Staining in 280 Eyes*

	Weight	
Time	5.5 Gm. (140 Eyes)	10 Gm. (140 Eyes)
Momentary	1.0	1.9

staining. Obviously, staining varies directly with both weight of the plunger assembly and duration of application, although the epithelium seems fairly resistant to slight pressure for a period up to ten seconds.

A wedge was removed from both plunger base [73] and base of the footplate of a Schiøtz tonometer. When this instrument was used on the cornea, pressure readings were not, of course, entirely reliable, but resultant disturbance of the epithelium showed that the plunger edge produced physical trauma. Th cornea stained where the weight of the plunger edge or the weight of the footplate assembly rested upon the surface. Where wedges were removed, there was no staining. In the plunger edge area particularly, it was observed that an incomplete circular ring occurred, staining readily everywhere except where there was no edge.

When the plunger edge of one instrument was somewhat rounded, it was apaprent that less staining occurred.

To show the effect of capillary attraction, methyl cellulose was dropped on a rubber balloon of approximately the size and tension of the human eye and tonometer readings recorded.

TABLE 6.—*Time: Average Staining in 420 Eyes*

	Time		
Load	Momentary (140 Eyes)	10 Seconds (140 Eyes)	20 Seconds (140 Eyes)
5.5 gm.	1.0	1.0	1.8

Methyl cellulose stronger than 1 percent is likely to give a higher scale reading; the reading may be still higher if the tonometer is repeatedly applied and more fluid allowed to climb into the space between plunger and sleeve. The effect of capillary attraction is less, of course, as the plunger load is increased.

TABLE 7.—*Capillary Attraction as Demonstrated by Tonometer Test Readings*

	Scale Readings			Per Cent Methyl Cellulose
Time	5.5 Gm.	7.5 Gm.	10 Gm.	
Momentary	6.0	6.5	7.0	0.0
	6.0	6.5	7.0	0.5
	6.0	6.5	7.0	1.0
	7.0	7.0	7.5	2.0

When methyl cellulose, 1 percent, was placed on the tonometer block, the reading was zero. It remained at zero with repeated applications. However, when 2 percent methyl cellulose was placed on the block, the readings were minus one or more except with the 10-gram load. This settled quickly to zero, but took longer and longer as repeated applications were made.

These experiments show that 1 percent methyl cellulose can be used on the cornea without appreciably affecting scale readings of the tonometer, but that higher concentrations are likely to invalidate readings on account of capillary attraction. It has been observed that capillary attraction is more likely to affect the scale reading in the Gradle-Schiøtz instrument than with the standard Schiøtz.

The silicones were discarded as a possible vehicle or protective substance because, by instilling them in my own eyes, I substantiated previous reports[35] that they cause a delayed conjunctival irritation.

Massage with a blunt rod, radius of curvature approximately 2 mm., caused no staining in the area of contact. Massage with a relatively sharper edge, radius of curvature about one-eighth of 1 mm., did cause staining in the massaged area. In each case, radiating folds from the pressure area could be seen under the slit lamp to take a fleeting stain during and after the release of pressure. On three occasions (6 eyes), tear droplets adherent to the blunt rod and to the relatively sharper edge were placed on a glass slide and examined under a microscope for epithelial cells.[69] None were found.

The 10-gram load was attached with cellulose tape to the back of the dial. Readings were the same with or without this load. The weight of the footplate assembly can, therefore, be considerably altered without appreciably affecting the scale reading. Adverse effect on the epithelium of this increased load on the footplate was not apparent. One must remember that the sharp edges of the footplate assembly do not ordinarily touch the cornea.

Experiments are going forward in an effort to find an anesthetic which will help to reduce staining of the cornea following tonometry. No positive results can be reported at this time.

Discussion

The part of the cornea receiving greatest trauma from the tonometer is the circular area indented by the plunger edge. The only circumstance in which this is probably not true is where intraocular pressure is so high that there is no indentation by the plunger which cannot emerge below the footplate.

Though it is inexcusable, I have had the plunger stick on attempting tonometry. In such instances, the disturbance is definitely increased because of trauma produced by the whole weight of the tonometer concentrated in the plunger area.

While it is probable that the greater staining usually seen at the plunger edge and in the plunger area is caused by the greater weight per square millimeter resting here, no proof can be offered. One cannot compare the plunger base and its load with the weight of the remainder of the tonometer on the footplate area for the reason that no one knows just what proportion

of the footplate comes in contact with the cornea. This contact area varies with many factors and, as Friedenwald has stated, "when the shape of the globe is distorted by indentation, the relations of surface and length to volume are no longer elementary."

Where there is staining corresponding to the rim of the footplate, it is probable that the tonometer has been tilted or the eye rotated, causing the relatively sharp edge of the base to come in contact with the cornea under some pressure. This can happen if the eye is not looking straight up or if the tonometer is not held vertically. Although epithelial disturbances are more evident in the area upon which the tonometer rests, and indeed most evident as a rule in the plunger edge area, they are by no means always so confined. They are less evident where tonometry is lightly and rapidly done and not repeated.

Staining areas assume variable sizes and shapes and may become confluent, even as one looks at them under the slit lamp. As blinking occurs, dry areas at once take up the green color of fluorescein. This appearance remains for a longer or a shorter period depending on the intensity of the drying effect. This is well seen at times even when no anesthetic has been used. It can often be made evident where the patient can willfully avoid blinking for a minute or two. It is greater after anesthesia than when an unanesthetized eye is held open for a similar length of time. Staining in any degree is infrequent, although not unknown, in the upper portion of the cornea where it is protected by the upper lid. This is due to two factors: there is less drying here because the cornea is kept covered and moistened, and less anesthetic reaches this area with the usual office method of instilling drops in the lower fornix. If care is taken to hold the upper lid up and away from the globe and the patient is asked to look down as the drop is placed above the cornea, and particularly if the lid and eye are held in this position for a moment or two, then just as much staining is seen in the upper portion of the cornea as anywhere else.[75]

The weight of the tonometer may affect the precorneal film. The splotchy staining characteristic of drying may not appear even after anesthesia and yet become obvious immediately after application of the instrument. Perhaps the weight alters the film in the area of pressure and predisposes it to separation and drying. As the precorneal film dries, it can be observed to split and retract, and one can actually see the development of irregular staining areas and sometimes dots which are similar to those seen in keratoconjunctivitis sicca. Kronning[42] has suggested, and I have independently observed, that one's interpretation of corneal disturbance must be modified according to whether the slit lamp was used prior to the employment of an anesthetic and the application of the tonometer.

The amount of disturbance will also vary to some extent with the time which has elapsed before slit lamp examination, and after an anesthetic has been used and the tonometer applied. There is more drying when the lids fail to blink because of anesthesia. While this is not entirely responsible for stains seen on the cornea, its influence upon the total picture cannot be disregarded.

Staining occurring from drying without anesthesia usually disappears within a few minutes. That following a local anesthetic may last several

hours. The precorneal fluid tries to avoid these dry areas and, although blinking temporarily covers them, the film soon separates again if the eye is kept open. So far as can be seen, only the epithelium is involved in these changes.

It is quite possible, as Cogan has suggested, that there is a close relation between pathology or disturbance in the endothelium, and the overlying epithelium. I have observed diffusion of fluorescein in the epithelium directly overlying edematous folds of endothelium. Sometimes staining is more pronounced over the area of mutton fat deposits in uveitis, however this is by no means always the case. It is of interest to note that rarely is staining seen where there has been previous injury or disease and scarring of the cornea.[26]

The question may logically be raised as to why, with identical techniques, some apparently normal corneas stain and others do not. Some corneas are sensitive to and adversely affected by local anesthetics. In such cases there is a definite stippling, sometimes involving the entire epithelium. This can be seen at times even before tonometry, and it is aggravated by the pressure of the instrument. It is also apparent that the general health affects the amount of staining. This has been so evident that I have come to delight in absence of staining in the eye being prepared for surgery.

In interpreting stains of the epithelium, one must be on the lookout for factors additional to anesthesia and the tonometer. For example, a misplaced lash can rub and irritate the cornea causing diffusion of fluorescein. Facial palsy, even a partial one, may result in exposure keratitis and consequent staining. One must also be sure he is not dealing with chronic conjunctivitis or keratoconjunctivitis sicca or punctate keratitis. He must also remember that staining can occur from the presence of a small filament of cotton or wool or even from disturbance caused by a blob or string of mucus. Staining may also occur after testing the cornea for sensibility with a cotton wisp, or when the finger touches the cornea in attempting to raise the lid or open the eye. Evanescent staining may follow rubbing the eye through closed lids, or may appear after simple squeezing of the lids. The staining seen in glaucoma and in flash burns could scarcely be confused with anything else.

When the eye is sensitive to the anesthetic, there is usually an intense spotty, splotchy, confluent, or diffuse staining observed after anesthesia and before tonometry. In such cases, the added trauma by the tonometer produces an even more intense reaction in the pattern of the footplate and plunger, especially where the plunger edge makes contact with the cornea.

Kronning[42] stated that disturbance produced in the epithelium from anesthesia and drying almost always has disappeared entirely at the end of three hours. The same is true of that produced during tonometry.

Where the precorneal film gives an impression of being abundant, and especially when bubbles are present in it, epithelial disturbance from tonometry is less likely to occur. There may be some correlation between this observation and that of Smelser[54] who found that there was less haziness of the cornea from wearing contact lenses when a bubble of oxygen was inserted beneath the glass.

Unquestionably the precorneal film is a protection to the cornea. It

appears to be practically impossible to remove this film completely by irrigating with normal saline. Three layers have been described. Two can be seen, the tear film and the lipoid layer covering it. The third seems somewhat theoretical, though I do not deny its presence.

The bow line of the tears along the lower lid margin and its covering grease film vary, but no relation of these factors to the susceptibility of the cornea to staining could be established. Clearing, sometimes following squeezing of the lids, may occur from expression of more lipoid, mucoid, and emollient material.

Surface disturbances of the corneal epithelium can readily be cleared to a great extent by glycerine, as reported by Cogan.[15] Swan [57] suggested that better results could be secured by a 2 percent carboxymethylcellulose spread directly on the cornea with a rounded glass rod. The simple instillation of a drop of 1 percent methyl cellulose is quite effective and less uncomfortable to the patient. If a stronger solution is used, the effect is to dry the conjunctiva, throwing it into folds and gumming up the eye with symptoms somewhat alarming to the patient, who experiences great difficulty in blinking. This can be relieved immediately by washing. While these substances will temporarily clear surface disturbances, they have no effect on diffusion of fluorescein around the site of a recently removed foreign body.

Among questions coming to mind regarding disturbance in the corneal epithelium after tonometry are the following: does trauma from the instrument produce a loss of cohesion between epithelial cells; are osmotic conditions in the cornea or its permeability influenced by the weight of the tonometer; does the arrangement of the hydrophylic micelles in the cornea, causing swelling to occur always in the antero-posterior direction, account for the sharp plunger ring stain so frequently seen; is normal water loss, in the area where there is no precorneal fluid, so interrupted that edema occurs here.

The factor of physical injury by the tonometer itself is important. The mechanical effect of this trauma may result in scuffing or in altered permeability of the superficial cells.[70] Whether this change is purely physical or is a physicochemical disturbance [39] is open to question. This problem is intimately connected with that of the cohesive quality of the individual cells [45] and whether this is disturbed by physical trauma or by chemical or neurological changes induced by the anesthetic used. In any event, it is certain that all topical anesthetics have a deleterious influence upon the epithelial structure [67] and obviously increase its vulnerability to the procedure of clinical tonometry.

I question the supposition that staining areas seen in the circumstances under discussion are edematous. Edema does not occur instantly. Furthermore, the fine edematous blebs seen in glaucomatous eyes do not stain until they are bruised or collapsed.

Due to technical reasons and changes undergone by tissues during processing, it is not possible to study these fleeting injuries under the microscope.[71]

The tonometer should be regularly inspected for imperfections. Many instruments are plated, and, when this plating flakes off, a rough margin

may be left on the footplate or plunger base which will cause damage—slight it is true, but potentially dangerous.

While the radius of curvature of the base of both footplate and plunger of the standard Schiøtz instrument is well designed for minimal trauma, it would seem that the plunger edge might be made less sharp and some injury avoided. Granted that this edge is most critical,[65] Schiøtz designed a tonometer with a plunger having a convex base which proved very satisfactory in excellent hands.[72] Well-known authors have declared that such an instrument is likely to be less dangerous to the cornea.§

Conclusions

Disturbance usually seen in corneal epithelium following tonometry is the result of trauma from the instrument added to the effects of local anesthesia. It varies in amount directly with age of the patient, duration of application of the tonometer, and weight of the plunger assembly.

Physical characteristics of the tonometer help to determine the amount and character of the disturbance.

The cornea can, to a measurable extent, be protected from tonometric trauma by instilling a drop of 1 percent methyl cellulose just before the instrument is used.

§ References 6, 7, and 52.

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Visual Effects Accompanying TEPP-Induced Miosis

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Pilots and others have long recognized the miosis which is frequently a consequence of spraying tetraethylpyrophosphate (TEPP) dust by aircraft. This effect of TEPP often occurs without symptoms referable to any part of the body except the eyes. Parathion (O,O-diethyl O-para-nitrophenyl thiophosphate) may also produce miosis, but it does so less frequently, and when it does the eye signs and symptoms are usually accompanied by general, systemic illness. The reason for the difference in clinical effect is not entirely clear but probably involves, among other things, the difference in molecular weight and vapor pressure of the two compounds.

Various flying accidents have been blamed on the effects of organic phosphates on pilots.* Two complaints which are occasionally made by the pilots themselves involve an inability to judge distance and a sensation that things are darker than the time of day, the season, and the weather justify.

A study in 1953 of the visual fields of 15 pilots and 2 other persons before, during, and after occupational exposure to TEPP did not reveal any meaningful change. However, only one pilot in this series was available for study of visual fields at a time when he actually had miosis. A much greater diversity of tests conducted during miosis seemed to be required to explain the reported disturbances of function.

The dosage level in the eye required to contract the pupil to 1 mm. diameter was worked out in an intensive study of one volunteer at three dosage levels. The study served to establish techniques for conducting a battery of ophthalmological tests. Instillation of 1 drop (about 0.01 cc.) of 0.0125% TEPP and later of 1 drop of 0.05% TEPP produced no measurable effect. Instillation of 2 drops (about 0.02 cc.) of 0.05% TEPP produced slight miosis and a slight increase of near accommodation. Maximal miosis was produced by 2 drops of 0.1% TEPP, the pupils being fixed at 1 mm. diameter. A fourth drop did not cause further miosis or other observed change. Visual acuity (Snellen), peripheral fields (Ferree-Rand simplified

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* References 1 and 4.

perimeter), depth perception (Howard-Dolman), color vision (Ishihara), and subjective perception all remained within normal limits. The near point as measured by the Prince Rule moved from a predosage distance of about 13 cm. to 3.8 cm. for the right eye and 4.5 cm. for the left eye.

The next logical course of investigation was to induce miosis in a number of pilot-volunteers. Six men with no previous exposure during the spray season in which the tests were made were selected from a group of commercial dusting pilots and their occupational associates by screening with a medical and ophthalmologic history followed by medical examinations.

The TEPP used in this experiment consisted of 40% tetraethylpyrophosphate and 60% related organic phosphates. Each drop (0.01 ml.) of 0.1% technical (40%) TEPP contained 0.009 mg. of technical TEPP in peanut oil. The maximum dose (2 drops of 0.1% into each eye) totaled 0.036 mg. For the average body weight of 83 kg., the maximum dosage rate was 0.0004 mg/kg.

For each dosage level, the volunteers were given batteries of tests at intervals of one hour. About one week elapsed between the different TEPP dosages. With the minor exceptions noted, each battery of tests consisted of the following 23 tests.

The first group of tests in each battery was performed with the Ortho-Rater † for far vision—(1) vertical phoria; (2) lateral phoria; (3, 4, 5) acuity, eyes together and separately; (6) binocular depth perception; (7) color vision—and for near vision—(8, 9, 10) acuity, eyes together and separately; (11) vertical phoria; (12) lateral phoria. A transilluminated Snellen chart and associated rheostat ‡ were used to make the following tests: (13) Bilateral acuity. (This was checked at the 20/20 level on all candidates with full power load in the chart-lamp circuit. Tests of more critical acuity were not in order because subsequent threshold tests required the use of the 20/20 test line, which was the only one homogeneously illuminated at various intensities.) (14) Threshold of light intensity required for reading. (Following the test of bilateral acuity, the light intensity was turned down by means of the rheostat until the volunteer could not distinguish the letters and then turned up until he could. The reading in arbitrary units, 135 for the entire scale, was recorded.) (15) Threshold of light intensity required for perception. (For the tests at the highest dosage level, 2 drops of 0.1% TEPP, the rheostat reading was also recorded at the first point at which the subject could distinguish the faint pinkish light in the chart, i.e., the threshold of minimum light perception. As the power delivered by the rheostat to the light circuit was reduced, the quality of the light changed from incandescent white to orange and then to a faint pinkish glow before disappearing entirely.) The Prince Rule and No. 3 Jaeger print card were used to test (16) accommodation for near vision. The Snellen chart and appropriate lenses held in the usual test frame were used to test (17) accommodation for far vision in respect to positive lenses; (18) accommodation for far vision in respect to negative lenses. A camera was used to record (19, 20) pupil size and reaction to light. (The eye was photographed in a darkroom with normal lighting. After adaptation in the dark for five minutes, the eye was again photographed.) The Hare perimeter was used to determine (21) field of vision. (Readings were taken for white on the vertical and horizontal axes of the perimeter.) The Schiøtz tonometer was used to measure (22) ocular tension. Blood was drawn from the ear to determine

† Bausch and Lomb Optical Company, Professional Model.
‡ Fisher Scientific Powerstat, Type 116, output range 135 volts.

(23) plasma and red blood cell cholinesterase levels, by use of a modification of the Michel electrometric procedure.[3] (Blood was drawn on two occasions before any TEPP was instilled into the eyes and again at the end of the last battery of tests at each dosage level.)

The results of the study are summarized in Table 1. Where there were

TABLE 1.—*Selected Ophthalmologic Measurements of Certain Functions of the Eyes of Pilots into Which TEPP Had Been Instilled**

Function	Condition of Test	Unit of Measure	Eye†	Dosage Level and Time After Dosage					
				1 Drop Peanut Oil (Control)		2 Drops 0.1% TEPP			
				Before Dose	After 1 Hr.	Before Dose	1 Hr.	2 Hr.	3 Hr.
Diameter of pupil	Illuminated	Mm.	L	5.4	4.6	4.5	1.9	1.9	1.8
	Dark	Mm.	L	6.7	6.6	6.5	1.9	1.9	2.0
Acuity	Minimum light to read Snellen 20/20	Rheostat units	B	33.3	33.2	29.7	35.5	32.7	33.0
Light perception	Minimum light (pink)	Rheostat units	B			12.9	17.8	17.2	16.4
Accommodation	Prince Rule	Cm.	L	13.3	13.3	12.3	6.1	6.8	7.9
	Snellen chart	Pos. diopters	B	1.58	1.62	1.92	2.25	2.46	2.42
		Neg. diopters	B	2.83	3.17	3.71	5.96	6.58	7.68
Acuity	Ortho-Rater, far vision	Ortho-Rater scoring units	B	10.8	11.8	11.8	9.5	10.2	10.0
			R	11.2	12.2	11.5	9.3	9.7	9.5
			L	11.2	11.5	12.7	9.8	10.3	10.7
	Ortho-Rater, near vision	Same	B	11.8	11.5	11.8	10.5	10.3	10.0
			R	12.2	11.0	12.5	10.0	10.0	9.7
			L	11.3	12.0	11.8	9.7	10.3	10.2
Depth perception	Ortho-Rater	Ortho-Rater units	B	6.7	5.3	6.5	6.2	5.8	6.3
Visual fields	Hare perimeter, horizontal	Degrees subtended	L	135.7	138.9	133.9	127.8	133.9	128.2
	Hare perimeter, vertical	Same	L	109.0	111.7	108.3	103.3	100.6	99.2
Ocular tension	Schiøtz tonometer	Mm. of Hg	R		19.3				16.5
			L		17.7				14.3

* Mean values from six subjects.
† Left eye, right eye, or both eyes, as indicated.

no notable differences in the two eyes, only data for the left eye have been given in the Table. Some tests which gave negative or normal results at all dosage levels have been omitted from the Table.

The production of maximal miosis, at least to the point of fixing the pupils, was considered one of the requisites of this study. Fixation of the pupils with concomitant effects was obtained consistently only with 2 drops of 0.1% TEPP spaced 30 minutes apart and not with a single drop.

Subjectively the maximum dosage caused mild headaches, sensations of pressure in the eyeballs or over the frons, slight burning of the lids, "running" or "stopped-up" nose, and a sensation that "things were getting darker." These symptoms passed their peak during the first or second hour. Four of the pilots stated, upon self-inspection in the mirror, that their pupils were not as small following the experimental exposures as they were following occupational exposure in the summer. One pilot believed that the experimental miosis was as severe as he had ever experienced in applying TEPP by airplane. The sixth man had had insufficient prior exposure to make a significant comparison.

At the highest dosage level, the subjective complaints of reduction of light perception were corroborated by the Snellen chart light-threshold test

and also by the minimum perception of light in the same back-illuminated chart.

The Prince Rule test showed greatest accommodation for near vision at the one-hour observation battery (30 minutes after the second drop). The lens test for far accommodation revealed a gradually increasing accommodation, particularly to negative lenses, at least until the third hour. One of the subjects was tested at the fifth hour also and was found to have undergone no further change in this respect. The changes in accommodation may be accounted for, at least in part, on a physical basis. The accommodation for near vision and for far vision with negative lenses is associated with the increased convexity of the lens of the eye as well as with the greater depth of focus which accompanies constriction of the pupil. The accommodation for far vision with positive lenses can be explained by the greater depth of focus which accompanies constriction of the pupil.

According to the Snellen measurement at the usual illumination, no change of acuity occurred at any dosage. But, as suggested above, some persons, after the 2-drop dose of 0.1% TEPP, noted that they required more intense illumination of the chart in order to achieve the same 20/20 acuity which they had before dosage, whereas, with the test conducted at unvaried illumination intensity, the Ortho-Rater showed a definite loss of acuity at the highest dosage level, averaging about 2 scoring units from 12 to 10 (Snellen equivalent of 20/17 to 20/20 for far vision), for both eyes and for each eye separately at both near and far vision. This slight loss of acuity was most evident during the period (one hour after dosage) when the patients were complaining most of the effects of ciliary spasm, conjunctivitis, rhinitis, and headache. It is quite possible that the chemical irritative effects as well as the diminished light intensity inherent in the miosis may have contributed to this slight loss of acuity.

Depth perception was not changed significantly at any dosage as measured objectively or by subjective complaints.

TABLE 2.—*Ocular Tension in Millimeters of Mercury as Determined by Schiotz Tonometer Before and After 0.1% TEPP*

Case No.	1 Hr. After Peanut Oil		3 Hr. After TEPP	
	Right	Left	Right	Left
2	19	19	13	13
3	26	17	28	17
4	17	20	16	15
5	25	20	17	15
7	13	13	12	12
9	16	17	13	14
Mean	19.3	17.7	16.5	14.3

Three hours after the administration of 2 drops of 0.1% TEPP, the average ocular tension of the six men dropped 2.8 and 3.4 mm. of mercury in the right and left eyes, respectively, as compared with normal levels established after instillation of peanut oil. The changes are summarized in Table 1 and given in more detail in Table 2. The tension of one man was a high normal after peanut oil and showed a paradoxical rise after only 1 drop of 0.1% TEPP. After the completely separate test with 2 drops of the same concentration, his tension was found to be back to his high normal level, and this same high normal level was still present one month after the last instillation of TEPP.

The averages of the tests for vertical and lateral phoria at near and far vision varied little. However, each of the subjects showed what appeared to be significant shifts in lateral phoria, but not all in the same direction.

Erythrocyte and plasma cholinesterase level, color vision, and perimetry remained normal throughout the entire experiment.

In order to be sure that the effects of the experimentally induced miosis were essentially the same as those of miosis acquired under conditions of actual application of TEPP dust, two pilot volunteers were reexamined during the season of occupational exposure. The rechecks were performed two to two and one-half hours after one pilot applied 2800 lb. of 1% TEPP (plus 1.5% other ethyl phosphates) dust and the other pilot applied 4900 lb. of the same formulation. One pilot showed no notable differences in the test results after the occupationally acquired miosis as compared with results after experimentally induced miosis. The second showed a greater ability to accommodate as measured by negative lenses at the usual Snellen test distance of 20 ft. His ability to read 20/20 was maintained up through − 7.00 D. compared with — 4.50 D. when his miosis was experimentally induced. However, as measured by the Prince Rule, accommodation was less than when miosis was induced. This second pilot also complained of loss of acuity in the right eye only ("has a shade over it" or "things look fuzzy"). The Snellen chart showed no detectable loss of acuity in this right eye, but the Ortho-Rater indicated a drop from his level with induced miosis of 10 to 4 scoring units (Snellen equivalent 20/20 to 20/50) for far vision. The left eye maintained the same acuity of vision after miosis was produced experimentally and occupationally. His acuity for near vision in the right eye dropped even farther after occupational exposure, from a normal of 10 scoring units to 1 unit (Jaeger equivalent: 1 to 10). The reason for this wide difference of results in the two methods of measurement is not yet apparent. It is believed that the repeated loss of acuity in the right eye of this particular pilot indicates a visual defect peculiar to his optical system.

By means of the several studies described thus far, physical explanations were found to account for all the predicted and recognized effects of TEPP in the eye. The one complaint by operating pilots remaining to be explained was their inability to judge distance with self-assurance. Dr. George H. Henton, Ophthalmologist, of Portland, Ore., who reviewed the results of the tests, suggested the possibility that radically unequal accommodation due to the production of miosis in one eye only might produce such effects. This hypothesis was consistent with clinical experience with patients who are placed on unilateral miotic therapy for the first time and also consistent with the infrequency of the inability to judge distance among pilots experi-

encing miosis after commercial applications. Moreover, several instances of unilateral miosis were discovered among pilots who were recently exposed as well as in old records of exposures.

As a test of this hypothesis, the first volunteer in whom bilateral miosis had been produced was retested with unilateral miosis following instillation of 2 drops of 0.1% TEPP. All ophthalmic results following unilateral induction were essentially the same for the single treated eye as they were for each eye following bilateral treatment. However, this volunteer did feel a little uncertain in going down or climbing stairways for about 12 hours after the instillation.

Six more nonpilot volunteers were given abbreviated testing after induction of unilateral miosis in the left eye. The objective findings were essentially the same (for the treated eye) as were those for the six pilots described earlier, but the volunteers with unilateral miosis had subjctive complaints for about 24 hours after the induction. Four of the subjects had no idea what minor disturbances of vision might occur. Because their subjective complaints are not easily subject to classification or quantitation, they are listed here.

CASE 1.—"Indefinable obscuring in the left field of vision and sensation that the two eyes were not on the same plane vertically."

CASE 2.—"The ground is coming up at me." "I feel one-sided." (The morning after induction, this volunteer hit his thumb three times in 20 minutes while attempting to nail fruit boxes. He has done this work for three months before and two months after this incident without such errors of distance judgment.)

CASE 3.—"The pegs are blurred" (on Howard-Dolman, but performance normal). "I feel like I'm stepping farther than I'm actually going. I'm giddy yet this morning." (This patient felt sweaty, especially on the back of his legs, about one and one-half hours after the first drop of TEPP. He was slightly nauseated and had tightness in his chest. He was nauseated by odor of ether while passing recovery rooms. This patient had been treated previously for neurocirculatory asthenia.)

CASE 4.—"It feels like it [the eye] is hanging out." "I feel like my left eye is wide open; it is bigger than my right eye and yet it feels like it does no good to look through the left eye." (This man missed the first step when reentering his home after the test.) "On the next afternoon I had the feeling that my left eye stared straight ahead, wide open and saw nothing. However, when I close my right eye, the image in the left looks O.K."

CASE 5.—"It feels cockeyed after the second drop." "I fumbled the sugar bowl, while removing it from a shelf at head height. I almost dropped it and I spilled sugar."

CASE 6.—"I have a vague feeling of not seeing too well." (This volunteer missed a step and almost fell.)

Thus, all seven of the volunteers in whom unilateral miosis was induced complained of subjective inability to perceive distance properly with self-assurance or experienced fumbling, stumbling, or other sensorimotor accidents or both.

Similar complaints frequently occur among ophthalmological patients in whom unilateral mioses is induced for therapeutic reasons. Dr. F. W. Jobe, of the Bausch and Lomb Optical Company, pointed out that these results are doubtless physiologically the same as the Pulfrich effect described by Duke-Elder [2] and in other textbooks. The Pulfrich effect causes the subject with unequal light intensities in the two eyes to perceive moving objects falsely; thus a pendulum appears to rotate in an ellipse instead of in one plane.

The induced or occupationally acquired miosis lasted from 12 to 24 hours, as indicated by the failure of the pupil to react to light and in accommo-

dation. Subjective complaints lasted about the same length of time. Partial constriction of the pupil lasted from two to three days.

Summary and Conclusions

Pilots and others have long recognized the miosis which is frequently a consequence of applying tetraethylpyrophosphate (TEPP) dust by aircraft. Accompanying the miosis, operating pilots have regularly noted a decrease in light perception and have more rarely experienced an inability to judge distance.

Two drops of 0.05% TEPP instilled into each eye of volunteers produced slight miosis and a slight increase of near accommodation.

Two drops of 0.1% TEPP instilled into each eye of volunteers produced maximal miosis, an increase in near and far accommodation, and a decrease in light perception but no inability to judge distance.

Two drops of 0.1% TEPP in only one eye of each of seven volunteers produced unilateral miosis and other expected changes in the treated eye but also caused all the volunteers to complain of difficulty in vision; four of the volunteers complained specifically of difficulty in judging distance, and six of them made sensorimotor errors of fumbling, stumbling, or other clumsiness.

It is concluded that infrequent unilateral contamination of the eye by spillage or other accident, accounts for the occasional inability of pilots applying TEPP to judge distance adequately. The incoordination which may accompany such inability to judge distance may be a serious threat to the pilots.

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Case Reports

ABSORPTION OF BOECK'S SARCOID IRIS NODULE WITH SYSTEMIC PREDNISONE

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THE CASE to be reported is of interest for several reasons: It is a case of Boeck's sarcoid iris nodule; the nodule was absorbed during systemic prednisone therapy; significantly higher systemic prednisone doses were given than have been hitherto generally utilized, and high systemic prednisone dosage was used in generalized sarcoidosis.

"Ocular involvement in sarcoidosis is both varied and frequent (Longcope and Freiman, 1952). The incidence is about 30 to 40 per cent. Almost all the structures in and around the eye may become involved: skin of the eyelid, eye muscles, orbit, uvea, and optic nerve. The commonest lesion is uveitis, which is usually painless and bilateral and may be accompanied by nodules on the iris."[3] In the evaluation of the therapy the statement of Duke-Elder should be kept in mind that "there is little tissue-reaction or tissue-necrosis and the disease very frequently subsides with great rapidity spontaneously, even large nodules disappearing to leave scarcely any scar."[1]

Report of Case

A 24-year-old Negro woman, two years prior to entry, following recurrent episodes of fevers, night sweats, nausea, vomiting, nocturia, exertional dsypnea, and occasional abdominal pains, with amenorrhea, weight loss, and blurring of vision, was examined and found to have generalized sarcoidosis with secondary bilateral iritis. There were generalized adenopathy and hepatosplenomegaly. Further investigation demonstrated a node biopsy positive for sarcoidosis, hilar adenopathy, negative tuberculin skin tests, typical phalangeal decalcifications, occasional increased serum globulin, occasional low white blood cell counts, variable sedimentation rate, occasional hypercalcemia, and hypercalcinuria, rare cylinduria and proteinuria, and normal electrocardiograms. An indentical twin sister gave a similar history without ocular involvement and with spontaneous relief from symptoms two or three years previously. Two courses of systemic cortisone of approximately one month's duration each (25 mg. four times a day) during the previous one and a half years had reduced her symptoms and signs temporarily. A course of local hydrocortisone relieved her eye symptoms temporarily.

The iris nodule (left eye) was first noted six months prior to entry for treatment. Upon entry it was noted to have maximum horizontal and vertical dimensions of 6 mm. and an average diameter of 4.5 mm.; it was whitish and cystoid, with small superficial vessels, and it occupied most of the angle of the inferior temporal quadrant of the anterior chamber.

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Los Angeles County Hospital.

Vision was 20/20 uncorrected in both eyes. Intraocular tensions and fundi were normal. Biomicroscopy showed the right eye to be normal; the left eye had old "mutton-fat"-like keratitic precipitates, 1+ flare (increased aqueous protein content), 3+ cells, scattered pigment particles on the lens, and minimal posterior synechia.

Fig. 1.—Boeck's sarcoid iris nodule before therapy.

The patient was placed on a general steroid supporting regimen including antacids, antispasmodics, supplementary potassium, and low-salt diet. Prednisone, 35 mg. (orally) every six hours, was started and was increased gradually to 50 mg. every six hours by the 10th day, following which it was decreased to zero by the end of the 14th day. The patient showed no ill effects during this period; weight remained essentially unchanged, and results of the following blood chemistry determinations were found to be within normal limits; albumin, globulin, calcium, phosphate, sodium, chloride, and alkaline phosphatase; however, the potassium was found on one occasion to be 3.7 mEq. (normal limits 4.1 to 5.6 mEq.). No local eye therapy was given except for 2% atropine drops to the left eye daily.

Findings on termination of the two-week course were as follows: almost complete absorption of the iris nodule, almost complete clearing of the flare and cells, absence of the previously palpable lymph nodes (adenopathy) and calcification, and reduction in size of the hilar nodes on x-ray as compared with x-rays of one year previously. ("It is recognized that metastatic calcification can be a complication of spontaneous or therapeutically induced hypercalcemia in sarcoidosis."[3]) Orbital x-rays disclosed no intraorbital or intraocular calcifications. Vision remained 20/20 uncorrected in both eyes, and the tensions remained normal. The hepatosplenomegaly was not present immediately prior to the therapeutic trial and was not present afterwards.

Fig. 2.—Boeck's sarcoid iris nodule after therapy.

Summary and Conclusions

A patient with generalized sarcoidosis with secondary iritis and iris nodule was treated with oral prednisone for two weeks (average dose, 40 mg. every six hours). The contraindications to high systemic prednisone dosage in generalized sarcoidosis seem to have been brought under question. Rate and degree of regression of general and ocular findings and absence of patient discomfort or complications are thought to be significant.

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Annual Reviews

STRABISMUS

Review of the Literature for 1955

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Proof has been given that strabismus is a prevalent disorder by a study conducted on the children in an English town of 75,000.[1] Of the population between 5 and 15 years of age, 2.7% had strabismus. Previously it had been estimated that 4% of humanity has a manifest squint.[2]

Basic Science Literature

Sensory.—The Hering-Hillebrand horopter deviation has been demonstrated to be due to the different distribution of retinal elements on the nasal side of the macula, as compared with the temporal side.[3] Conclusions are based on the differences in the threshold of stereoscopic acuity between myopes and emmetropes.

A somewhat new concept of the horopter has been presented.[4] Actually, two horopters are suggested—objective and subjective. The former is the fixation horopter, associated with corresponding points of the retina of each eye. The latter is the projection horopter, the site to which images are projected that are formed on the cyclopian retina.

I have been enlightened by Ogle's [5] distinction between transverse and vertical image disparity that will produce fusion (within Panum's fusional space) and stereopsis. Both horizontal and vertical limits of image disparity that permit stereopsis are greater than those that permit fusion. His experiments indicate that the maximal vertical image disparity permitting stereopsis is greatest at the fixation point, while it is greatest in the peripheral retina for horizontal image disparity.

Again this past year there were a few reports suggesting that a sensory component does exist in the nerves innervating the extraocular muscles. Specialized nerve endings were described which might record the tension of the muscles and tendons.[6] Also, afferent impulses were recorded ascending the oculomotor nerve.[7] With a microelectrode responses were detected in the medulla oblongata, pons, and midbrain when an inferior oblique muscle was passively stretched.[8]

Motor.—A new concept in the motor portion of the innervating system serving ocular motility has been introduced as an eye-centering system.[9] There is both experimental and clinical evidence for such a system. For instance, electrical stimulation of certain cortical areas or subcortical pathways causes eye movement either away from or toward the center. The quick component of nystagmus represents normal function of this pathway; diseases of the basal ganglia associated with fixed straight-ahead stare are irritative lesions.

Criticism has been directed at Perlia's nucleus actually having any connection with the medial recti, on the basis of examination of midbrains of monkeys which had the integrity of their oculomotor nerve interrupted at either orbital or intracranial level.[10]

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Attention is called to the definition of the meter angle as defined by the committee on optics, American Academy of Ophthalmology—the angle formed by the two visual axes at a point of fixation 1 meter from the center of the interocular base line.[11]

Some interesting facts concerning accommodation have been provided by an ingenious method of photographing the Purkinje-Sanson images during scotopic vision.[12] It was deduced that accomodation is set off by a stimulus detected by cones and not rods. The accommodation tends to remain, in the absence of any stimulus, approximately 0.6 D. (the questionable cause of sky myopia and night myopia), fluctuating rhythmically ±0.3 D., searching to ascertain whether vision will be improved by stimulating or relaxing accommodation. Accommodation is proportional to the degree of sharpness that the vision need be; the greater amount of accommodation being present while the subject is reading small rather than large Snellen letters through a −5 D. lens.

There is some evidence that a position of rest exists when the visual axes are slightly convergent, suggesting that convergence and divergence control ocular alignment from this neutral position.[13] Progressively increasing alcohol intoxication caused a corresponding increase in esophoria at 600 cm. and increasing exophoria at 33 cm., with the visual axes coming to a position of rest at the 60 cm. intermediate point. As expected, a weakening of the vergence movements was concomitantly noted with increasing blood alcohol levels. This was manifest by the longer time required before fusion movements were initiated and increasingly remote convergence near point.

Testimony that electromyography is rapidly advancing as a research and clinical tool is obtained from the increase of articles on this subject from Europe, Japan, and the United States. Thus far the following statements have been electronically proved: (1) primary position is not, innervationally speaking, a position of rest; (2) the laws of Hering and Sherrington are valid; (3) divergence innervation increases when the intermittently divergent strabismus patient becomes exotropic.* Paresis of an ocular muscle can be diagnosed and recovery can be followed by electromyography.† Nystagmus potentials have been demonstrated.‡

The literature pertaining to the aspect of motility that deals with ocular torsion is comprised of somewhat conflicing reports. There have been some descriptions of true and false (apparent) rolling of the eye about the anterior-posterior axis when moved obliquely away from the primary position.§ Opposing this point of view, Quereau [23] finds there is no torsion during oblique fixation except when the eye is moved obliquely in the temporal field beyond 25 degrees from the primary position. Then the eye rolls outward about the anterior-posterior axis when moved obliquely upward and rolls inward when moved obliquely downward. The explanation for the conflicting reports may be found in differences of methods used in studying this problem. The former group of workers appear to be using planar coordinates, whereas Quereau uses spherical coordinates.

A normal rectus muscle has been found to be capable of lifting a 60 gm. weight (weight of eyeball is 7 to 8 gm.[24]). Normally the lateral and medial recti are of

* References 14 and 15.

† References 14-17.

‡ References 14, 15, and 18.

§ References 19-22.

equal strength. In exotropia the lateral recti are preponderant, whereas the medials are strongest in esotropia. A paralyzed muscle is totally lacking in lifting power, or nearly so.

A scheme for demonstrating function and binocular coordination of extraocular muscles as well as a method of analysis of comitant and noncomitant strabismus by objective (prism and cover) and subjective (diplopia studies) methods has been presented by Sternberg and Raab.[25]

Sensory Complications of Strabismus

Amblyopia.—Twenty million squinters are estimated to be found among the five hundred million inhabitants of Europe, sixteen million having esotropia, of which three odd million have an amblyopic eye.[2]

With the aid of fundus photography it is possible to identify exactly what part of the amblyopic retina is used for fixation,[26] which is helpful in establishing a prognosis for visual improvement. Stable eccentric fixation is capable of improvement, but if there is extreme variation as to which area of the retina is used therapy of any type does poorly.

Amblyopia does not disturb the normal electroencephalographic tracing, regardless of whether the intermittent stimulus of light is projected into the good or into the amblyopic eye.‖

New ideas about the treatment of amblyopia reflect various degrees of condemnation of the time-honored routine of occlusion. Some feel that patching is justified only in the event that the amblyopic eye is capable of macular fixation,[28] that it only intensifies pseudomacular fixation[29] and offers little to no chance of improving vision when the eccentric fixation is constantly changing. Patching is completely condemned by Nemetz,[20] who reiterates all claims previously made by Bangerter to the effect that there is no need to occlude the good eye. In addition to its possibly enhancing paramacular fixation, he advances such hardships as tape reaction due to skin sensitivity to the adhesive, discomfort during summer months, behaviour problems, peeking, and lack of parental concern, understanding, and fortitude as reasons for not instituting a patching program. He claims great success for Vienna clinic after having used Bangerter's technique for two years. Instead of being patched, the child attends amblyopia school two to three sessions (one hour each) per week for three months.

Opposed to discarding the simple, inexpensive patch remedy for amblyopia, the average ophthalmologist continues to start occlusion of the good eye at a very young age and despite minor hardships does a good job of equalizing the vision in the two eyes.¶ Success is not 100%, but neither is it by Bangerter's or Nemetz's method. Although it must be conceded that visual stimulation exercises hasten the improvement, such added therapy does not increase the chances of visual improvement. To illustrate this point, Francois and James[34] treated differently two groups of 100 cases each, chosen at random from 1800 cases of strabismus. The first group received occlusion only; the second was given visual stimulation exercises in addition to occlusion. The end-results were the same, although 68% of the exercised group needed only 4 weeks to attain what 69% of the unexercised group gained in 14 weeks.

‖ References 26 and 27.

¶ References 30-33.

An ingenious method of treating deep amblyopia, as found in eccentric fixation, by simultaneously depressing the pseudomacula with an exactly focused bright light and stimulating the macula by appropriate stimuli is being tried.# Restoration of good to normal vision has been reported in 25% of such cases.[35]

Suppression.—Suppression is an active purposeful repression acquired by the young squinters.[38] It eradicates two things: (1) diplopia, resulting from the object of regard being projected onto the noncorresponding areas (macula of fixating eye and pseudomacula of deviating eye); (2) visual confusion, caused by two different objects, one of which is the object of regard, being simultaneously projected onto each fovea.

An area of relative or absolute scotoma can be plotted in one eye only while the opposite eye is fixating, and the phenomenon of suppression is confined to the scotomatous area.[38] The scotoma always includes the macula and pseudomacula, and usually the intervening area between the two. It is elongated horizontally, with the macular side being a sharply delimited vertical line, bisecting the fovea, except for a variable-sized macular bulge extending across the hemiretinal line. The magnitude of the macular bulge is proportionate to the degree of amblyopia.[38]

There are quantitative and qualitative variations within the scotomatous area, but the most deeply suppressed spots are the macula and pseudomacula. Suppression may be so delicate that it can be detected only if similarly contoured images are simultaneously presented to each retina. On the other hand, it may be so deep as to be almost absolute; suppression of the image in the deviating eye occuring regardless of whether dissimilar contours, different colored lights, targets of different illumination, or even moving targets are used.[38]

Once visual maturity has established itself (approximately age 6) prior to the onset of a paretic strabismus, the second image of diplopia can only be "ignored," but not suppressed.[38] No suppression scotoma can be outlined in the deviating eye of a squint that started during or after late childhood.

The nature of the test used to elicit suppression and the depth to which this sensory adaptation to strabismus has developed determines the subjective response of the patient. Since, as Jampolsky[38] states, suppression is so often a subtle and alterable sensorial anomaly, any test to detect it should simulate casual everyday seeing. He says, "This qualification is not met in many of the complex clinical and laboratory testing situations, with consequent confusion resulting. It is superfluous at times to depend upon an artificial laboratory experiment which may lead to misinterpretation of the facts of suppression when common sense deductions may be more profitable." He deducts that if a patient with manifest constant strabismus does not experience double vision while fixating a light in the primary plane, suppression exists. To outline the scotomatous area he increases horizontal and vertical prism power, by using the Risley hand prism before the deviating eye, to the point that diplopia is experienced. Also, by testing with multiple-contoured similar targets in a major amblyoscope or using a twin Polaroid projection apparatus, the zone of suppression can be demonstrated and measured.

A latent period is required for suppression to become manifest.[38] A brief flashing exposure by cover test or flashing of a major amblyoscope may eliminate the suppression, producing momentary diplopia. Retinal correspondence tests are frequently made possible by utilizing this latent period.

References 35-37.

In disagreeing with the clinical importance that Swan has placed on the "blindspot mechanism," Verhoeff [39] points out how such a mechanism does not do away with visual confusion, nor with all diplopia outside the blindspot area. True, under artificial laboratory conditions, the blindspot mechanism prevents diplopia for a small object within a blank patternless visual field. However, this is far removed from everyday seeing conditions, and Verhoeff believes that the only way these patients with small-angle esotropias are comfortable and not complaining of visual confusion and diplopia is by the existence of suppression and abnormal retinal correspondence. He emphasizes that artificial laboratory tests, such as those done on a stereoscope, amblyoscope, or haploscopic device, do not always give answers compatible with the way the strabismic child actually solves his sensory visual problems.

Treatment for suppression can be either preventive or active, or possibly a combination of the two. Suppression can be prevented from developing or deepening simply by occluding one eye. It is doubtful that any degree of suppression is reversed by this procedure.

Orthoptics is an active form of therapy. In fact, orthoptic treatment of suppression is being rendered each time the measurements of the scotomatous area are repeated with the Risley prism. Elaboration of this method is the very technique used by orthoptists in treating suppression.[38] Each successive measurement usually reduces the size of the originally outlined scotomatous area.

The orthoptist takes advantage of certain fundamental characteristics of suppression while treating it. By rapidly covering-uncovering the deviating eye in a continuous rhythmical fashion, permitting the eye to be exposed to the object of regard for less time than the latent period required for suppression, diplopia recognition of the object of regard is augmented. Furthermore, if at the same time the fixation light is made to appear dissimilar to each eye, which can be accomplished by introduction of a red filter before the deviating eye, suppression of the pseudomacula is overcome even more readily.[38] Often, very brief training suffices to make the patient capable of calling forth, maintaining, and surrendering diplopia as he wishes, first with and eventually without the aid of flashing and red filter. This type orthoptic program is open to certain criticism, since it can be considered partial in a sense that only the pseudomacular suppression is treated, while the macular suppression is ignored.[40]

A major amblyoscope affords an orthoptic onslaught upon the suppression that compensates for both diplopia and visual confusion. In order to make the treatment with a haploscope as physiological as possible, it is advisable to stimulate bimacularly with similar foveal targets and at the zero angle with dissimilar targets.[40]

As a result of more and more emphasis being placed upon straightening strabismic eyes at a young age or the soonest possible time after onset, suppression is having an increasingly difficult time of establishing a firm foothold. Surgery is good for both preventing further deepening of suppression as well as actively treating the suppression scotoma. The visual axes, however, should be adequately moved so that postoperatively the object of regard falls on the side opposite to the hemiretinal line which borders the suppression scotoma.[38] Then the previously suppressed area along with its corresponding area in the fellow eye will be, while seeing under everyday visual circumstances, bombarded with identical contoured images. What better active treatment is there for suppression?

Abnormal Retinal Correspondence.—Unlike amblyopia, which is a uniocular anomaly, suppression and abnormal retinal correspondence (ARC) are anomalies of binocular vision.* Suppression and ARC are very inter-related, and it is even suggested that ARC is merely one of the characteristics of suppression.[38] ARC develops only in the presence of suppression, and it is logical to entertain the idea that it represents one of the more advanced and complicated adaptations to diplopia and visual confusion, whereas suppression is one of the less advanced and simple adaptations. Suppression demands a latent period after fixation is established before it solves diplopia and visual confusion, but ARC requires no latent period.[38] Perhaps this is just one reason why the sensorial adaptations deviate far away from normal retinal correspondence (NRC) in their attempt to offer the squinter a good form of second-rate binocular vision.

As in the case of suppression, most ARC tests yield conflicting and confusing results because they are artificial laboratory procedures. There is usually little resemblance between the test employed and the everyday seeing conditions confronting the patient.† It may be that unharmonious ARC reports are due to this unfortunate fact.[38] It is not too preposterous to suspect that the strabismic child either relies upon suppression while maintaining NRC, or depends upon harmonious ARC to solve his diplopia and visual confusion. Just what unharmonious ARC can accomplish for him escapes reason. Could it not be that such a report typifies a confused patient, who is facile at using either NRC or ARC? Not knowing which sensorial localization system to use under laboratory seeing conditions, he allows the NRC and ARC to compete with one another, and a meaningless blend of the two is reflected in the peculiar test result we classify as unharmonious ARC.[38]

Despite the questionable results obtained by ARC tests, progress is being made in improving this situation. The ideal test for clinical purposes should encompass the following: (1) require little intelligence in the subject being tested; (2) not be time-consuming or exhaust the patient or examiner; (3) not require special instrumentation that is expensive, cumbersome to operate, or unavailable[43]; (4) be capable of testing ARC even if the subject suppresses[38]; (5) simulate everyday seeing conditions.[39] The major amblyoscope probably affords the simplest, quickest, and most fluid and interesting method of testing for ARC. Moreover, by flashing and using dissimilar targets the suppression problem can usually be circumvented.[38] Its principal shortcoming is found in the fact that it is a laboratory instrument and consequently does not simulate everyday seeing conditions.[39]

Treatment of ARC, as in the case of suppression, involves preventive and active therapy. The best preventive measures entail some steps that do away with the two factors that cause ARC: (1) strabismus in a young child that has (2) both eyes in the open. Straightening the eyes, by surgery if necessary, at a very young age and occlusion of one eye eliminates these factors.[42] There should be no fear of operating in the face of ARC, since ARC does not automatically preclude a good result.‡ Paralleling the visual axes by

* References 41 and 42.
† References 38 and 39.
‡ References 44 and 45.

surgery is good active ARC therapy, but it is not always successful.[42] Orthoptic results have been notoriously poor.§

Motor Complications of Strabismus

Since the medial recti have been found to have greater lifting power than the lateral recti in esotropia and vice versa in exotropia, contracture or hypertrophy of the converging or diverging muscles, as the case may be, is thought to develop as the strabismus persists.[24] Also, the direct antagonist of the involved muscle in paralytic strabismus undergoes contracture.[47]

Heterophorias

Often a clear-cut line cannot be drawn between a phoria and a tropia. At one time a case may be a phoria and at another lapse into a tropia. Similarly, at a certain distant or near point of fixation or direction of gaze either a phoria or a tropia may be present, but the opposite may exist when the subject is fixating at a different distance or in another direction. Furthermore, there is actually little difference between phorias and tropias in regard to diagnosis and therapy.[48] However, in phoria there is always fusion, which may be lacking in tropia. In their struggle to gain fusion, the phoria patients are more prone to be uncomfortable than those with tropias. Phorias tend to progress to tropias, but the reverse is not true. For this reason, a phoria may need surgical correction early, before binocular vision is lost.[48]

Horizontal Phorias.—Patients with convergence insufficiency are frequent sufferers of headaches, vertigo, and asthenopia. Their symptoms must stem from near fixation, since 50% are known to be near emmetropia and orthophoric while fixating at distance.[49] Orthoptics is the best treatment for this condition.‖

Vertical Phorias.—Vertical phorias are frequently in combination with lateral phorias.[48] Careful work-up of the patient usually identifies the faulty cyclovertical muscle, which is mandatory if proper surgery is to be done. One surgeon will advocate strengthening the weak muscle,[51] while another will be adamant over weakening its direct antagonist, or yoke. Since binocular vision is almost spontaneous if proper surgery has been done, postoperative orthoptics is not indicated. Orthoptics does not cure incorrect surgery.[48]

Comitant hyperphoria, if not too great, may be treated by prismatic correction [52] or orthoptics. Success [53] and failure [46] are both claimed to be the expected result for hyperphoria treated with orthoptics. The average result probably falls somewhere between these two extremes—some patients being helped and others not.

A hyperphoria is described by Lebensohn [54] which he calls innervational hyperphoria and attributes to a tonic motor inhibition of a cyclovertical muscle caused by wearing spectacles for anisometropia. The eye with the greatest plus or least minus in the vertical meridian must make the greater movement on looking downward. The fellow eye receives a tonic motor inhibition, and with increasing age this tends toward an increasing hyper-

§ References 32, 42, and 46.
‖ References 46 and 50.

phoria. Diagnostically, innervational hyperphoria is suggested by the following: a constant vertical phoria for all lateral positions of gaze; no primary and secondary deviation; having worn a spectacle correction for anisometropia for some time. An issue is made of correcting the near rather than the distant phoria with prism. Other suggestions to correct this innervationally induced hyperphoria are different size lenses, slab off, dissimilar segments for the bifocal wearer, or various combinations of these methods.

Accommodative Esotropia

The cause-and-effect relationship between hypermetropia and accommodative esotropia has been well documented,¶ but hypermetropia is not the only etiologic factor. Often overlooked is the peculiar type of association of accommodation and convergence frequently encountered in accommodative esotropia. If the esotropia increases while the subject is fixating approaching objects, the deduction is valid that the association of accommodation and convergence is not usual or of the normal type. Otherwise, the alignment of the visual axes would be practically the same for all points of fixation, either distant or near. But if a small amount of accommodation innervation, barely sufficient to increase the refractive power of the lens by 1 D., evokes an exaggerated convergence, for example, as much as 15 D. of convergence, such an abnormal association of these two phenomena is certainly contributing to esotropia whenever the child accommodates.[60]

The abnormal type of accommodation convergence association and hypermetropia frequently work together, one accentuating the other, in producing accommodative esotropia. However, it is well to keep in mind that either of these etiologic factors may cause accommodative esotropia unassisted by the other. For example, there is the emmetropic child whose eyes are "straight" at distance but "crossed" at near fixation as contrasted to the large hypermetrope who is esotropic while not wearing spectacles by the same amount whether looking at a distant or a near object. Yet the moderate hypermetrope, whose esotropia is small at distance fixation, increasing significantly as nearer and nearer objects are viewed, suffers both etiologic factors.

It is an enigma why an infant should develop, or innately possess, an abnormal association of accommodation and convergence. One suggestion attributes this difficulty to accommodation being suddenly discovered at a time while the ciliary muscles are immature and weak. Strong accommodation impulses must be dispatched which are associated with abnormally strong convergence impulses.# Such theses are near impossible to prove or disprove. Spasms of accommodation, associated with miosis, are known to cause esotropia in older children. However, this is not the type of accommodative esotropia encountered in younger children, since the duration of the strabismus is measured in terms of minutes or seconds. Such disorders are considered to be functional.[63]

The part heredity plays in this problem is most prominent.*

Onset of intermittent convergent strabismus at approximately age 1 year

¶ References 55-59.

References 61 and 62.

* References 56 and 57.

or later, the greatest incidence being between 1½ and 2½ years, is the typical introduction to this problem.† Since a high percentage of the untreated change from intermittent to constant esotropia, an aggressive therapeutic program started early after onset has the best prognosis.‡ To head off the development of constant esotropia, with its resultant surrendering of bifoveal fixational ability (see fixation disparity), amblyopia, suppression, abnormal retinal correspondence, and muscle contractures, is the worthy objective of early therapy.

Cycloplegic refraction can be done at any age, and it is helpful to bear in mind that after hypermetropic spectacles have been worn for some time subsequent refractions often reveal greater hypermetropia than was disclosed by the initial refraction.[58]

In addition to glasses, the opthalmologist should list weak-strength isoflurophate (DFP) in the therapeutic armamentarium for accommodative esotropia.§ Very little accommodation innervation is required to effect a large amount of accommodation when the eyes are under the influence of isoflurophate. Consequently, very little convergence innervation is evoked, which has a dramatic beneficial effect on accommodative esotropia. In concentrations between 0.025% and 0.0125%, one drop (about 0.06 cc.) daily in each eye often controls the strabismus. If some caution is exercised to adjust the concentration so that the pupil is allowed to expand somewhat within 24 hours prior to the next instillation of isoflurophate, the complication of "cysts" on the pupillary margin of the iris may be lessened. If "cysts" do develop, they promptly disappear when medication is discontinued. Isoflurophate is helpful in the very young child with no significant anisometropia or astigmatism. Also it can conveniently be used to aid in deciphering what part, if any, of the esotropia is accommodative in nature. However, for the long-range haul of controlling the new accommodative esotrope, isoflurophate is not threatening the established reputation earned by spectacles.

Many writers grapple with the problem of a greater esotropia for near than for distance. Opinions regarding therapy range from surgery through bifocals and dissociation orthoptic exercises [37] to use of isoflurophate,‖ some advising one or the other singly while others advocate various combinations or else nothing. It apparently is not too unpopular in England to do surgery if the eyes are straight for distance fixation but crossed for near.¶ But it is brought into sharp focus by writers in this country that only the esotropia present while the patient is fixating at distance with glasses should be operated upon if postoperative divergence is to be avoided.[55]

Bifocals are very useful for this problem,# but there, again, objection is raised to their use on the basis that difficulty is encountered in removing them once the patient has become reliant upon them.[67] Orthoptics is suggested along with bifocals,[55] but usually this problem is prevalent at an age too young for orthoptics. At an older age, dissociation exercises are helpful in getting the child out of bifocals.

† References 57 and 58.
‡ References 57, 58, and 64.
§ References 65 and 66.
‖ References 65 and 66.
¶ References 46, 64, and 67.
# References 58 and 66.

Isoflurophate, oftentimes in addition to the distance spectacle correction, controls the excessive convergence that occurs while fixating at near.

If the refractive error is not too vast, the need for glasses to control the accommodative esotropia vanishes sometimes with no additional therapy.[58] Almost never does this occur prior to 7 years of age. Probably the majority, however, require some added treatment, either in the form of orthoptics (dissociation exercises)* or a program of using diminishing concentrations of isoflurophate before they escape glasses.

Orthoptics exerts its beneficial effect by increasing the amplitude of fusional divergence to the point that it exceeds the excessive convergent alignment brought on by accommodation. Then, granted the patient is willing, by applying sufficient fusional divergence, the accommodative esotropia is neutralized while the vision remains clear. This may prove fatiguing to the child, particularly while doing prolonged reading, and for such cases part-time wearing of glasses will be required. Needless to say, the need for dissociation exercises deserves careful judgment by the ophthalmologist. Excluded from orthoptic therapy should be large hypermetropes, astigmats, and anisometropes.

Another therapeutic approach is to lessen the convergent alignment by diminishing the accommodation innervation. This can be done without blurring the vision by using weak strength isoflurophate. By this method the convergent alignment present when glasses are removed may be reduced to the point that it is less than the fusional divergence amplitude which, if the patient applies it, will straighten the eyes. Cutting the isoflurophate from 0.025% to 0.0125% and then to 0.00625% over a period of a few weeks to months, with use of 1 drop daily in each eye, gradually controls the accommodation less and less. As more and more accommodation is required to obtain clear vision, increasing amounts of convergence gradually develop that must be corrected by the fusional divergence if straight eyes and clear vision are to be maintained. In an attentive patient over age 7 the fusional divergence will usually meet these increasing demands successfully and through necessity thereby increase its amplitude as effectively as if an organized program of dissociation exercises had been carried out.

Nonaccommodative Esotropia

In 1951 Keiner published his idea that defective myelination of the visual pathways may be a factor in causing squint. Increasing interest is being shown to this contention,† despite the inherent difficulties in proving it. There might be some substantiation of Keiner's idea if any importance is attached to the prevalence of strabismus amongst children afflicted with neuropsychiatric disorders.[69]

The diagnosis is not always as simple as one would think. Not only must nonaccommodative esotropia be unraveled from accommodative esotropia, but, further, it must frequently be differentiated from pseudostrabismus. Epicanthi, narrow interpupillary distance, and negative angle kappa,[70] singly or in combination, are little foolers that considerably increase the importance of doing the cover test before being so confident as

* References 45 and 67.

† References 59 and 68.

to diagnose esotropia. And the heteronymous fixator (fixates with the right eye in the left field of gaze and vice versa) challenges the ophthalmologist to differentiate nonaccommodative esotropia from bilateral lateral rectus palsy.[71]

Many extol the virtues of doing surgery to correct nonaccommodative to differentiate non-accommodative esotropia from bilateral lateral rectus esotropia during infancy.‡ Early opportunity to use normal sensorial retinal relationships and to fixate bifoveally affords the best chance of spontaneous development of single binocular vision. The longer the strabismic child persists in using noncorresponding retinal areas and fixates with one fovea, causing the sensory and motor complications of strabismus to deepen, the less the chance of spontaneous single binocular vision developing when the eyes are straightened.

Despite the unanimous expression favoring surgery during infancy, two different opinions have been presented as to the specific age surgery should ideally be done, yet each opinion is based on the same premise—that binocular reflexes are underdeveloped during the first year of life. One cites this as reason for there being little gain in doing surgery prior to 15 months of age,[44] while the other considers this to be the reason why it would be ideal to do the surgery between 3 to 6 months of age.[67] Apparently surgeons have in mind the age range of from 8 months[60] to 2 years when they speak of early surgery. I would estimate the average as being between 15 to 18 months of age.

Only one writer cautions against early surgery. On the basis of Thorner's previous report of 50% less strabismus among 5000 school children between ages 12 and 13 as compared with ages 5 to 6, Weve[77] believes that the strabismic child has 50% chance of spontaneous improvement.

Consideration should be given to the details involved in doing the surgery. The emotional trauma inflicted upon the little child can be negligible if the hospitalization is made as brief as possible, the mother permitted to stay with the child, and the eyes left unpadded postoperatively.§

Ophthalmic surgeons are all not in accord as to the best method of correcting esotropia. Since tightening the lateral rectus does not increase the abduction ability to the same extent that recessing the medial rectus diminishes the adduction power, combining both procedures on the same eye may result in eyes which are straight in the primary position but which develop exotropia when looking in the field of action of the recessed medial rectus and esotropia when looking in the field of action of the tightened lateral rectus. Therefore, asymmetrical surgery produces asymmetrical results which may be an unnecessary barrier to a functional result.[44] For this reason symmetrical surgery (tightening lateral recti or recessing medial recti) is advised.‖ Despite these established facts, many surgeons feel that the recession-resection procedure on the same eye gives better predictable and more consistent results.¶ Two further advantages are cited: (1) one eye is left unoperated on, in the event

‡ References 37, 44, 46, 59, 64, 67, and 72-76.

§ References 37, 46, 64, and 78.

‖ References 44, 46, 75.

¶ Reference 79 and Kestenbaum, in discussion on Schlossman and Shield,[58] Am. J. Ophth. 40:118-119 (July) 1955.

that a second operation is indicated at a later date, and (2) the surgeon can learn by doing the first eye in what manner the patient responds to a certain amount of surgery, which might be helpful prior to doing a second procedure, on the eye not operated on the first time.[55]

When a cosmetic result is all that can be hoped for, such as in a case of intractable amblyopia, unilateral surgery on the poor eye is preferred.# Owing to the drifting of the visual axes into a position of divergence with advancing age, it is best to anticipate this by intentional slight undercorrection of the esotropia in which a functional result is a known impossibility.[37]

This past year's literature contained about three significant reports dealing with surgical technique. Foggitt[80] introduced a procedure of partially crushing and partially myotomizing the strong medial rectus or recti in congenital esotropia. O'Connor[81] redescribed his cinch operation. Hiroishi[82] coordinated his surgery with electromyographic studies on the muscles to be operated on.

Teaming orthoptics with surgery continues to be a popular way of handling nonaccommodative esotropia.* Orthoptics is felt to be of benefit in esotropia of less than 25 degrees when the vision is nearly equal and fusion is possible at the objective angle.[45] Ideally, the patient should be over 6 years of age.† Then, in no more than 12 sessions, preoperatively and postoperatively, suppression should be eliminated, diplopia established, and fusional amplitudes increased.[45]

One important point is becoming increasingly clear—it is better to start therapy and be aggressive (surgery) at a very young age rather than be conservative (waiting for orthoptics).[76]

Because postoperative diplopia increases after 8 years of age, some opposition is expressed toward using orthoptics after this age in children having ARC and/or no fusion at the objective angle.[83] Ill-advised orthoptics in this type of case may increase the risk of postoperative diplopia, diplopia resulting from incapacity for fusion, or paradoxical diplopia due to persistent ARC.[84]

In the event the child is too young for orthoptics or surgery, depressing the neurovegetative system by prescription of sedation has been recommended.[85] The merit of such therapy is not apparent to me.

Fixation Disparity

Many years ago Panum described a definite and measurable space on the horopter, seen by one eye, that surrounds the center fixation point of the opposite eye. Any point within this space, that is viewed by one eye, may have the identical directional value assigned to it that is given to the central point fixated by the fellow eye. Dependent upon this basic physiological fact, that an object need not be imaged absolutely onto corresponding retinal points in order to be fused, is the clinical syndrome of fixation disparity. Just so long as the object of regard is projected within a certain area surrounding the fovea of the deviating eye, it is capable of sharing the same spatial localization given to it by the fovea of the fixating eye.

References 44 and 77.
* References 44, 45, 54, and 73.
† References 44 and 54.

This means that even though a minimal deviation of the visual axes exists, such as a small esotropia, despite bifoveal fixation of the object of regard being precluded, fusion of the object of regard is possible. Consequently, the object of regard is not simultaneously localized at two different points in space (diplopia) if the esotropia is a fixation-disparity syndrome. As to what extent the eyes may be convergent, yet the object of regard still be projected onto the area of the deviating retina that corresponds directionally with the fovea of the fixating eye, I am uncertain. A few years ago Swan gave the amount as being up to 8 D. and this figure appears reliable from a clinical standpoint.

There is variance among writers as to what the fixation-disparity syndrome encompasses, but on the essential features of absence of bifoveal fixation and presence of fusion all are agreed.

The next most accepted feature of the syndrome is a mild amblyopia of the deviating eye. This sensory complication likely results from suppressing the fovea of the deviating eye in order to escape visual confusion (simultaneously seieng two different objects clearly, located identically in space). Such reasoning presupposes that retinal correspondence is normal, and the majority recognize this to be so.‡

An additional clinical feature often observed in fixation disparity is the application of the vergence reflex for the purpose of reducing the deviation of the visual axes sufficiently to permit this syndrome to be present. This is detected by comparing the difference between the cover-uncover measurement and alternate cover determination, the esotropia often being much greater than 8 D. by alternate cover test but not more than 8 D. by cover-uncover test.§ The difference between these two determinations is representative of the magnitude of fusional divergence movement required to control diplopia by utilizing Panum's fusional space. The alternate cover test measures the fusion-free position, since binocular vision is impossible with either one or the other eye covered. Often the fusion-free position of the esotropia is greater than that which will permit fixation disparity (8 D.). The cover-uncover test measures the everyday binocular seeing position of the eyes, since both eyes are in the open while fixating a designated object prior to covering of the foveally fixating eye. If the deviating eye moves no more than 8 D. in order to establish foveal fixation, the fixation disparity syndrome could have been present.

The question is unanswered as to why a patient with good divergence ability will reduce a covergent alignment of the visual axes to less than 8D. but will not go all the way to attain bifoveal fixation.

Once the patient has surrendered bifoveal fixation and/or adapted to its absence, all agreé it is almost impossible to retrieve.‖ Orthoptics for this problem appears to be wasted effort.

The fixation-disparity syndrome is by no means a small and minor portion of the total strabismus problem. With advancing years, more ophthalmologists and orthoptists are recognizing that an increasingly large number of

‡ References 86-89.
§ References 55 and 87.
‖ References 46, 86, 88, and 89.

their patients eventuate into this category.¶ Fortunately our concern is abating over the seriousness of not enjoying bifoveal fixation while experiencing fusion as we become more reconciled to accepting such a result as good.[67] The patient has always been delighted with such an ending, from both a cosmetic and a functional point of view.[88] Fixation disparity does not increase the chance of postoperative divergence as the patient ages.[80]

Divergent Strabismus

The primary factor in causing divergent strabismus is a hereditary bilateral anomaly, strengthened by such secondary factors as myopia, anisometropia, widely separated orbits, and fusion defects.[56] However, one careful study of a large number of exotropes indicates that the refractive errors of divergent strabismus parallel those of the general population, only 22.8% being myopic.[90]

Divergent strabismus usually has its clinical onset during the first several months to years of life.# Early in its clinical course it is manifest only at distance fixation and then but intermittently, the exotropia by alternate cover test being less at near than distance. With increasing age the exotropia at near tends to increase until it may eventually equal or exceed the distance measurement[67]; particularly is this so if the fusion mechanism has difficulty in coping with the divergent malalignment. If there is a well-defined obstacle to clear vision in one eye a constant uniocular divergent strabismus is likely to develop at a very young age.[90] Otherwise, the intermittent divergent pattern either tends to remain on into adulthood or very gradually fades into constant divergent strabismus in the older children.

The upward deviation of a constantly diverged eye is attributed to the normal anatomical position of rest being one of divergence and elevation.[92]

Opinions vary considerably about therapy, ranging from doing nothing to surgery: one advises minus lenses[93]; some expound the merits, others the limitations of orthoptics.

The majority that recommend surgery are in no hurry to operate*; in fact, most surgeons seem to have a self-made rule that the intermittently divergent strabismic patient first attain an arbitrary minimum age before they will operate. Most often this age is listed as somewhere between 9 and 12 years. Rather than use an arbitrary age, it may be more fitting to consider the need for surgery in the light of the symptoms experienced by the patient and the attitude of the parents toward the problem, against the background of whether the ophthalmologist feels the divergent strabismus will spontaneously improve or not.[94] Subjective symptoms of the patient are diplopia, confusion, asthenopia, difficulty in sunlight, and embarrassment of having a "wall eye." The parents may be worried or annoyed about frequently observing the following: (1) diverged eyes, occurring when the little patient is (*a*) visually inattentive (day dreaming, thinking of a fast excuse, at the peak of an emotion), (*b*) unwilling to put forth the fusion effort required to straighten the eyes (upon first awakening from a deep sleep, fatigue, illness); (2) closing or covering one eye, especially while in sun-

¶ References 37 and 86.

Knapp, P., in discussion on Schlossman and Boruchoff.[91]

* References 37, 44, 64, and 67.

light. It is the aggregate of all three factors: (1) the severity of the patient's symptoms, (2) the extent of the parents' concern, and (3) a realistic appraisal by the ophthalmologist as to the likelihood of there being ultimate need for surgery that can best determine when the surgery should be done, even if it means doing the surgery at a very young age.

Here again, as in esotropia, the plea is strong for symmetrical surgery,[44] with preference being divided between weakening the lateral recti[46] and tightening the medial recti.†

The value of orthoptics in treating this problem cannot be assigned a final rating yet. Whether it is in the best interest of the patient, considering the divergent strabismus from the point of view of the total life span of the patient rather than simply during childhood, to encourage self-conquering of this annoying problem by solely prescribing orthoptics[96] or to attempt total eradication by surgery, thereby making orthoptics unnecessary, cannot be wholly appraised in an open-minded manner at present. Disappointment over the absence of a lasting cure having been rendered by orthoptics, with ultimate correction by surgery, is frequent.[46] Yet the exact reverse to this statement is far from unknown. Perhaps this is why many intentionally combine orthoptics and surgery and claim best results by such a method.‡ However, if the merits of surgically attempting to do away with this problem while the child is very young, below the age that orthoptics could be recommended, become established, orthoptics may ultimately be used in the role of the ace in the hole, to be applied to those resistent cases not cured solely by surgery.

Horizontal Noncomitant Strabismus

The associated ophthalmological findings of an acquired brain stem lesion are likely to be a third nerve palsy, a sixth nerve paralysis,[97] an internuclear ophthalmoplegia, or Parinaud's syndrome[98]—all in the absence of papilledema.[97] In regard to etiology of a brain stem lesion, tumor, demyelinating disease, and vascular lesion all cause the same signs; differentiation is only disclosed by history, clinical course, and associated findings.[98]

Sixth nerve palsy in the presence of papilledema suggests a cerebellar tumor.[97] Increased intracranial pressure as a cause of sixth nerve palsy is challenged by Murray,[97] who thinks it is more probable that the nerve is stretched over the tumor.

There should be no hurry to operate in cases of noncomitant strabismus in an attempt to control diplopia. Waiting for the diplopia to stabilize deserves prime consideration.§ When surgery is performed it is better to do a small amount with the possibility of doing several procedures rather than risk overcorrection.[99] Emphasis should be put on striving to attain orthophoria in the inferior field, since this is essential for the patient's comfort.[99]

Vertical Strabismus

Comitant.—The vertical component is frequently encountered in horizontal strabismus. Surgical correction of the vertical factor is just as important

† References 67 and 95.

‡ References 44, 46, and 95.

§ References 99 and 100.

as correction of the horizontal if a fusional result is to be expected.[44] The orthodox surgical approach of the vertical portion of the strabismus is to work on one or more of the cyclovertical muscles. Another approach to the same problem is the suggestion of raising or lowering the insertions of the horizontal recti operated on for the horizontal squint.‖

Noncomitant.—It is not difficult to understand how ocular torticollis compensates for the diplopia caused by a cyclovertical muscle palsy. Yet it is not understood why some cases of cyclovertical muscle palsy, devoid of any fusion ability, manifest ocular torticollis. Manzitti and Ciancia [108] discovered the head tilt to vanish in 10 cases of superior oblique paralysis, regardless of whether fusion was present, when the involved eye was occluded. Occlusion of the sound eye had no such effect.

Surgery in paralytic strabismus is indicated for one or a combination of the following reasons: (1) cosmetic improvement, (2) to eliminate torticollis, and (3) to enlarge or move the field of fusion.[47] The interplay of two contradictory factors decides when surgery is desired: (1) spontaneous recovery and (2) the desire to restore parallelism of the vision axes as soon as possible. Surgery is advocated at a very young age when the paralysis of the muscle is congenital if binocular vision is to be maintained with assuredness or if the hope be that binocular vision will develop.[104] Permanent changes in the bones and muscles of the neck and face that are induced by torticollis can only be avoided by early surgery.[104]

The convictions various surgeons have on whether the paralyzed muscle should be strengthened are quite contradictory. Some claim that such a procedure ends in almost certain failure,[47] and others proclaim it as the procedure of choice, especially when dealing with superior oblique paresis.¶ For the same diagnosis, tenotomy of the ipsilateral inferior oblique and recession of the contralateral inferior rectus is advised by one [107] and only weakening of the inferior rectus by another.[108] For inferior oblique palsies, two advise resections of the involved muscle and tenectomy of the homolateral superior oblique, yet one goes further and also recommends recessing the opposite superior rectus,[109] while the other cautions against weakening the superior rectus for fear of a restricted field of vision.[110]

Overaction of the inferior obliques, associated with horizontal strabismus, commands attention of many authors. Conjecture is great in attempting to explain this condition. It has been blamed on the convergent alignment of esotropia causing contracture of the more powerful inferior obliques as compared with the weaker superior obliques.[92] This does not help us to understand why we frequently see overaction of the inferior obliques in divergent strabismus. Another speculation is that a weakness either of the superior obliques or of the superior recti is in the background,[111] which can be differentiated by using the Bielschowsky head-tilt test. Despite the pathogenesis of this condition being obscure, it probably is not due to a congenital weakness of the superior obliques, because it has been observed to develop in accommodative esotropes who did not squint until late and in children lacking binocular vision, as in high anisometropes.[112] Hypoplasia of the malar bones, causing an antimongoloid slanting of the palperbral fissures and

‖ References 101 and 102.

¶ References 105 and 106.

an S-shaped contour of the lower lid margin, occurring in a patient whose visual axes diverge on elevation and converge on depression, will often result in overaction of the inferior obliques regardless of whether there is esotropia, exotropia, or no strabismus.#

The majority advise surgery for overaction of the inferior obliques, practically all advising a myotomy or recession to be done on those muscles.*

Overaction of the superior obliques complicating a divergent strabismus is a not uncommon syndrome. It has been attributed to weakness of the inferior recti.[116] The divergence tends to build up to gigantic amounts when the eyes are depressing straight downward from the primary position. Shekter [116] advises resection of the inferior recti combined with the horizontal surgery for this condition.

Congenital shortening of the tendon sheath of the superior oblique, as described by Brown, simulating inferior oblique weakness, has been observed by Nutt [104] in 36 patients. Forced duction test under anesthesia reveals limited upward movement while the eye is adducted. The procedure of choice is tenectomy of the superior oblique.[104]

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

I. S. Tassman, M.D., Chairman
William Krewson, 3rd, M.D., Clerk
Jan. 19, 1956

An Eye with Endothelial Dystrophy and Multiple Malignant Melanomata: A Histopathologic Case Report. WILLIAM C. FRAYER, M.D.

The case of a 59-year-old woman with bilateral endothelial dystrophy and a progressively enlarging melanoma of the iris and ciliary body was followed for five years. After enucleation of the left eye, a second malignant melanoma was found in the choroid which had not been noted clinically. These two malignant melanomata were thought to be independent primary growths. Histopathologic studies also revealed corneal changes characteristic of cornea guttata, or endothelial dystrophy.

A review of the literature revealed only one previous report of multiple primary malignant melanomata in a single eye which appeared to fulfill the criteria for independent tumor growth. Only eight previous histopathologic reports of eyes with endothelial dystrophy could be found in the literature.

Turbidimetric Measurement of Streptococcal Antihyaluronidase in Uveitis and Primary Glaucoma. JOSEPH W. HALLETT, M.D., and IRVING H. LEOPOLD, M.D.

Hemolytic streptococcal hyaluronidase evokes antibody formation. Nongranulomatous uveitis is said to be principally due to hemolytic streptococcal infection. Increased antihyaluronidase activity of the blood has been reported in chronic simple glaucoma. In this study blood serum antihyaluronidase levels were determined turbidimetrically in 326 normal persons, 90 patients with uveitis, and 40 patients with chronic simple glaucoma. Thirty-two of the uveitis cases had follow-up determinations of the levels performed. No increase in the geometric mean titer over that of the normal controls was found in any group. The index range difference (IRD) indicated very slight value of the test only in nongranulomatous uveitis. Fluctuations in the titer may be of more significance in uveitis than a single test.

Ophthalmology in India. RICHARD A. ELLIS, M.D. (by invitation).

While working with various missionary ophthalmologists in villages of India and Pakistan during the 1954 to 1955 season, I noted many differences in the practice of ophthalmology from that in the United States. The reasons for these great changes in our specialty are due to the social and economic conditions in that part of the world. There is an acute shortage of well-trained physicians, and poverty is extreme. Many of the people are superstitious, and the caste system, though outlawed, still exists in the villages. The practice of quackery flourishes. Approximately 90% of the people are illiterate, and sanitation is practically nonexistent. Facilities for transportation and communication are primitive. The weather is favorable only one-third of the year, and it is either too hot or constantly rains during the remainder of the year. Therefore, the great majority of patients are treated during the four months of the winter. When a patient does present himself for treatment, one therefore treats him to the fullest extent, since it is unlikely that the patient will ever again see a trained ophthalmologist for the rest of his life.

Besides all of the diseases that we have in the United States, there are many eye conditions which are rarely found in our country. There are many cases of vitamin A deficiency with the typical findings of night blindness, xerosis, Bitot's spots, and keratomalacia. Trachoma seemed to be present in the overwhelming majority of the patients that I examined. There are

also many cases of leprosy and smallpox with eye involvement. Ocular infections are commoner because of the lack of sanitation and the unavailability of antibiotics. The incidence of glaucoma may be more frequent owing to the greater number of cases of the untreated secondary types. Cataracts also appear to be more numerous in this section of the world, and the end-results of some couching operations done by the quacks are occasionally seen. It is noteworthy that no cases of retrolental fibroplasia were seen.

The great bulk of the practice of ophthalmology consists of eye surgery. Cataract extraction is the most frequent operation performed. During the winter months usually from 20 to more than 100 cases are operated on a day. Three operating tables are used at the same time so that there is no loss of time. The surgeon goes from table to table. Usually cataracts are removed bilaterally at the "same sitting." The nurses give the local anesthesia, and occasionally, if needed, the surgeon repeats the anesthetic injection. Graefe knife incisions are most popular, and three corneoscleral sutures are used in each case. The patients are discharged after 8 to 10 days of postoperative care, at which time the sutures are removed. Most patients are given a simple +10 spherical lens unless they request a complete refraction. Any complicated cases are kept as long as needed. Glaucoma surgery is the second commonest type of ocular procedure. Because the patients will not use miotic therapy, the diagnosis of open or narrow-angle glaucoma would be the indication for glaucoma surgery. Plastic repair for entropion secondary to trachoma is the next most frequent type of surgery. Dacryocystorhinostomies and optical iridectomies are other surgical procedures. Because of religious beliefs, enucleations are very rarely performed.

Eye surgery is performed in "eye camps" as well as hospitals. In these "eye camps" from 50 to a few hundred operations are performed in one to two days. This surgery takes place in tents or small buildings in the villages, and the patients are also followed for 8 to 10 days. In spite of all the handicaps, the operative results are very gratifying.

The treatment of eye disease may vary in the large cities. However, since 85% of the population is concentrated in rural areas, I believe that the picture that I have presented is more indicative of the practice of ophthalmology in India.

I. S. Tassman, M.D., Chairman
William E. Krewson, 3rd, M.D., Clerk
Feb. 16, 1956

Surgery of Congenital Cataract with Special Reference to Complications of Surgery. PAUL A. CHANDLER, M.D., Boston.

The subject was discussed from the standpoint of indications for operation, optimum time for operation, choice of operation, and complications of surgery.

In bilateral complete or nearly complete cataract, operation is done on one eye under one year of age. If no complications are encountered with the first eye, the second eye is then done. If operation on the first eye is followed by serious complications, operation is deferred on the second eye until the child is 2 or more years of age. In cases of lamellar cataract, unless the opacity is obviously so dense as to preclude useful vision, operation is deferred until the child is old enough for an accurate determination of visual acuity, usually 5 to 7 years of age. If corrected vision is 20/50 or better, operation is not done. The handicap of somewhat defective vision is to be preferred to accepting the hazards of surgical interference.

As to choice of operation in infants with a dense opacity, iridectomy, inferior iridotomy, and linear extraction is advocated, whether or not the pupil dilates well preoperatively. It is believed that fewer complications

occurred after this procedure than any other. In the case of lamellar cataract in older children, a good result may be obtained with various procedures. My preference is linear extraction with iridectomy, as resulting in fewer complications in a large series than other procedures.

Of the complications during operation, vitreous loss with linear extraction is the most serious. The incidence of this complication is greatly lessened if firm pressure on the globe is maintained for five minutes before the operation is begun, in order to soften the globe. Great care in application of forceps, expressing lens cortex, and irrigation of the anterior chamber is very important.

Of the postoperative complications, an inadequate pupillary opening, glaucoma, and retinal detachment are the most serious. An adequate pupillary opening is difficult to secure if the pupil becomes small or drawn up. It is felt that the operation of full iridectomy, inferior iridotomy, and linear extraction results in less difficulty in obtaining a satisfactory opening, especially in younger patients. The importance of long-continued use of atropine after operation is stressed. Topical use of steroids is important if the postoperative reaction is severe.

Glaucoma can occur from swelling of the lens and closure of the angle after discission. It is avoided by making a wide opening in the capsule so that the lens does not swell as a whole. Lens cortex may block the filtration meshwork and cause glaucoma. Treatment of these forms of glaucoma is prompt linear extraction.

Pupillary block is the most important cause of glaucoma after congenital cataract surgery. It is recognized in some cases by a frank iris *bombé*. In other cases there is unevenness of depth of the anterior chamber. The most characteristic sign is gross peripheral synechia extending well out onto clear cornea in one or more places. (Slides) Early recognition and early treatment are essential if the eye is to be saved. Treatment consists in peripheral iridectomy or iridotomy. This is completely effective if done in time. A case is presented in illustration. In neglected cases all vision is usually lost in spite of repeated surgical attempts. If discission must be done in the presence of a small pupil or in any case of pupillary block, peripheral iridotomy should be done at the same time to avoid block of the pupillary opening by vitreous.

Detachment of the retina may occur as a late complication of congenital cataract surgery. Results of operation for such detachment are relatively unfavorable. A serious problem in this connection is inability to see the peripheral fundus owing to a small pupillary opening. The possibility of late detachment of the retina is an argument for full iridectomy in congenital cataract surgery so that the fundus can be better visualized and all the retinal breaks found.

The difficulties of congenital cataract surgery are stressed. It is felt that such surgery should properly be performed only by the most skillful and experienced surgeon.

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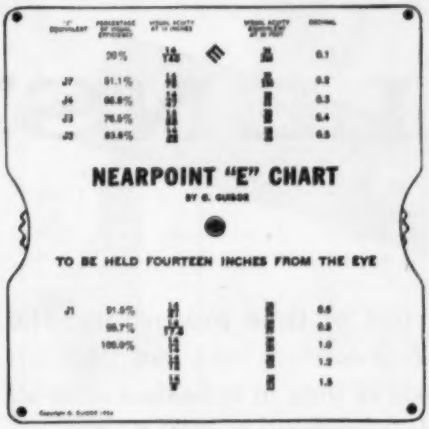

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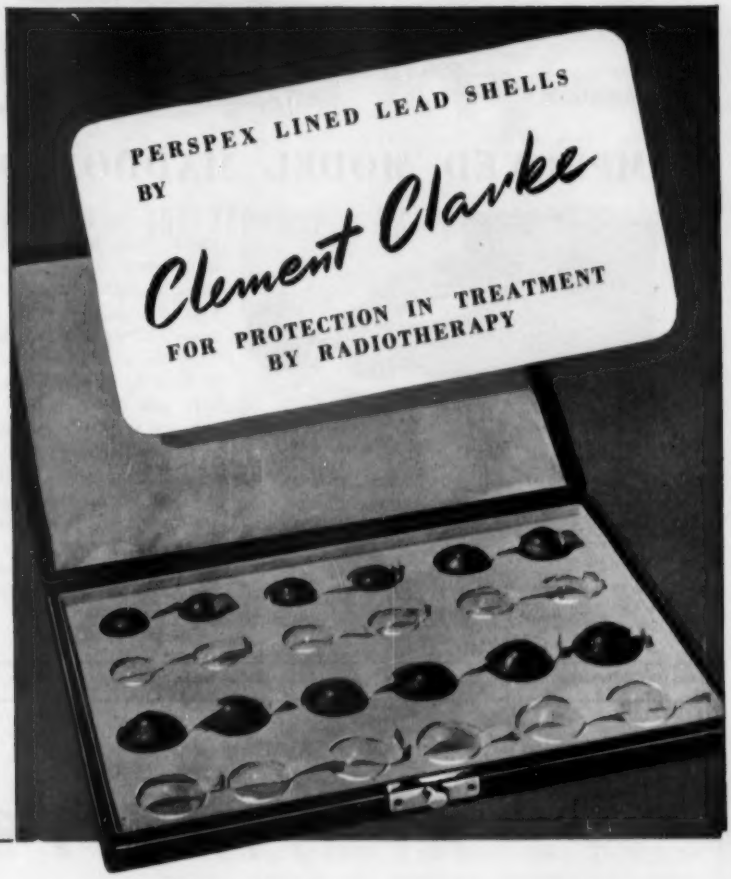

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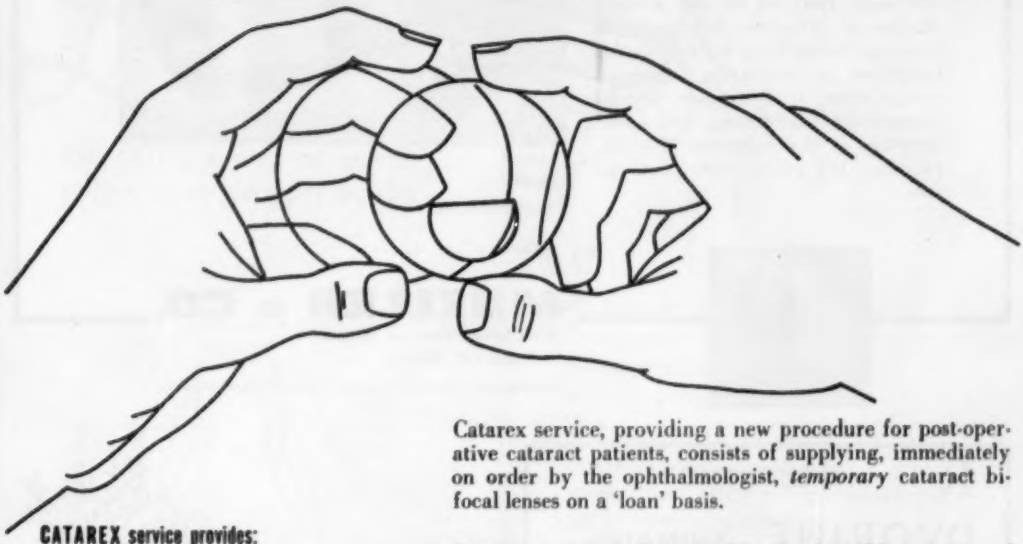

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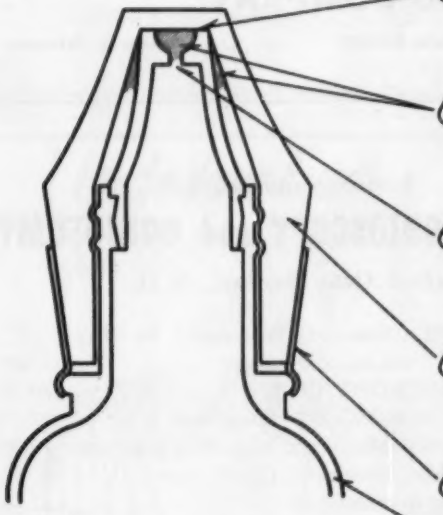

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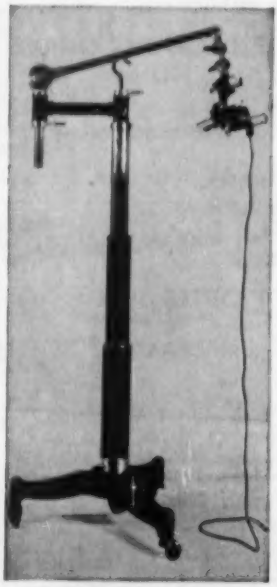

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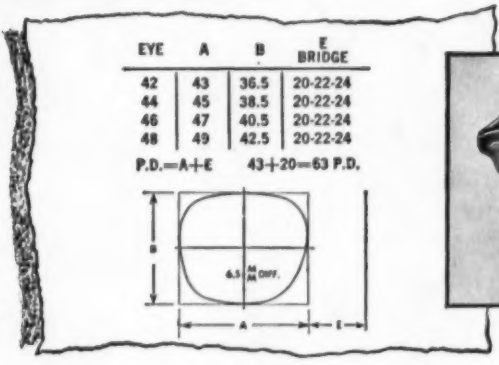

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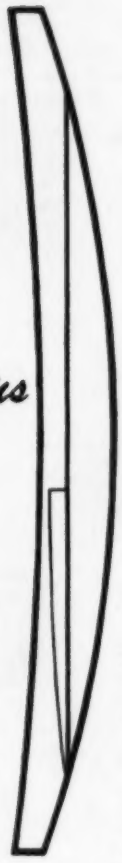

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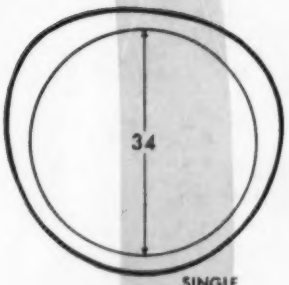

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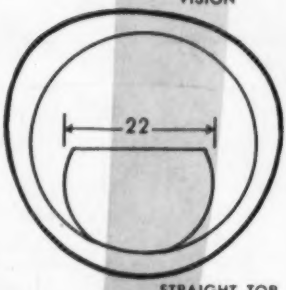

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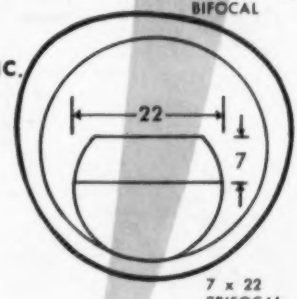

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